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Abstract

Improvements in military trauma care during the wars in Afghanistan and Iraq have contributed to increased survival rates for combat-injured American military personnel. Yet, little is understood about the short- and long-term physical and mental health symptoms resulting from these injuries. Understanding clinical presentations and symptom trajectories in survivors of complex combat injuries is paramount to the future development and implementation of interventions that are capable of reducing the disabling effects of symptoms and, subsequently, improving health outcomes across the continuum of trauma care. This dissertation addresses the key question: in an era of unprecedented survival after complex and life-threatening injuries, what are the short- and long-term symptom trajectories of post-traumatic stress disorder (PTSD) and pain, even after exposure to pain management interventions, specifically regional anesthesia (RA)? Furthermore, this investigation evaluates the effectiveness of RA on reducing pain intensity after injury. To address these inquiries, this dissertation used the longitudinal data from one of the largest and most comprehensive datasets of patient-reported outcomes from American military personnel and veterans wounded in action during Operation Enduring Freedom and Operation Iraqi Freedom. Principle findings were: 1) There is an established association between pain and mental health symptom presentations in combat-injured military personnel and veteran populations that exists throughout care settings where nurses are practicing; 2) PTSD symptom severity, and pain intensity and interference are significantly correlated up to twenty-one months after injury; 3) Worsening PTSD symptom trajectories are associated with higher pain intensity after injury compared to improving or stable PTSD symptom trajectories; 4) Early receipt of RA for pain management following combat injury is associated with improved patient-reported pain outcomes; 5) Markov chains are a practical method for characterizing probabilistic pain trajectories after combat injury, and can be beneficial in future work to examine the benefits of analgesic interventions. Results inform future directions for advancing nursing science research and directing practice, in the context of implementing interventions to manage pain after serious injury in order to maximize recovery across military, veteran, and civilian populations.

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FROM THE FRONTLINE TO THE COMMUNITY:

THE USE OF REGIONAL ANESTHESIA AFTER COMBAT INJURY AND ASSOCIATED PAIN OUTCOMES

Nicholas Alfred Giordano

A DISSERTATION

in

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2018

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FROM THE FRONTLINE TO THE COMMUNITY:

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Nicholas Alfred Giordano

DEDICATION

This dissertation is dedicated to the brave men and women of the United States Armed Services who safeguard and transmit to posterity the principles of justice, freedom and democracy.

But in silence, in dreams' projections,
While the world of gain and appearance and mirth goes on,
So soon what is over forgotten, and waves wash the imprints off the sand,
In nature's reverie sad, with hinged knees returning I
enter the doors – (while for you up there,
Whoever you are, follow without noise and be of strong heart.)

Excerpt from "The Dresser"
Drum-Taps (1865)
By Walt Whitman

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ABSTRACT

FROM THE FRONTLINE TO THE COMMUNITY:

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Nicholas A. Giordano

Rosemary C. Polomano, PhD, RN, FAAN

Improvements in military trauma care during the wars in Afghanistan and Iraq have contributed to increased survival rates for combat-injured American military personnel. Yet, little is understood about the short- and long-term physical and mental health symptoms resulting from these injuries. Understanding clinical presentations and symptom trajectories in survivors of complex combat injuries is paramount to the future development and implementation of interventions that are capable of reducing the disabling effects of symptoms and, subsequently, improving health outcomes across the continuum of trauma care. This dissertation addresses the key question: in an era of unprecedented survival after complex and life-threatening injuries, what are the short- and long-term symptom trajectories of post-traumatic stress disorder (PTSD) and pain, even after exposure to pain management interventions, specifically regional anesthesia (RA)? Furthermore, this investigation evaluates the effectiveness of RA on reducing pain intensity after injury. To address these inquiries, this dissertation used the longitudinal data from one of the largest and most comprehensive datasets of patient-reported outcomes from American military personnel and veterans wounded in action during Operation Enduring Freedom and Operation Iraqi Freedom. Principle findings were: 1)

There is an established association between pain and mental health symptom presentations in combat-injured military personnel and veteran populations that exists throughout care settings where nurses are practicing; 2) PTSD symptom severity, and pain intensity and interference are significantly correlated up to twenty-one months after injury; 3) Worsening PTSD symptom trajectories are associated with higher pain intensity after injury compared to improving or stable PTSD symptom trajectories; 4) Early receipt of RA for pain management following combat injury is associated with improved patient-reported pain outcomes; 5) Markov chains are a practical method for characterizing probabilistic pain trajectories after combat injury, and can be beneficial in future work to examine the benefits of analgesic interventions. Results inform future directions for advancing nursing science research and directing practice, in the context of implementing interventions to manage pain after serious injury in order to maximize recovery across military, veteran, and civilian populations.

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CHAPTER 1

Introduction

Since the terrorist attacks on September 11, 2001 in the United States (U.S.), over 2.5 million American service members deployed to engage in counterterrorism efforts globally.[1] Service members operating on the front-lines of combat zones encounter modern warfare weaponry, including high intensity weapons and improvised explosive devices (IED) that have the potential to inflict unprecedented injury patterns and severity.[2,3] During the past 17 years of these global conflicts, more than 50,000 service members have been wounded in action.[4] Many of these service members have sustained a multitude of injuries across several organ systems and anatomical regions of the body, known as polytrauma.[5] For the first time in U.S. warfare history, the majority of these combat wounds are survivable despite their magnitude and severity, largely due to advancements in military trauma care.[6] This survivability means individuals are living with serious injuries that were previously considered fatal. Therefore, changes are needed in the management of both acute and chronic injury-related pain. Moreover, little is understood about the long-term physical and mental health symptom trajectories among survivors of polytrauma.

Progress in combat casualty care extends to military hospital care and comprehensive rehabilitative service where the toll of warfare is evident in both the visible and invisible wounds of war. Chronic pain and post-traumatic stress disorder (PTSD) are frequently observed together among veterans returning from Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF).[7,8] Estimates show 30% to 68% of injured OEF/OIF

veterans experience symptoms of PTSD, and over 80% report experiencing chronic pain.[9-11] Chronic pain is associated with PTSD, functional impairment, behavioral health issues, and compromised health-related quality of life.[12-14] Combat-injured military personnel report worse pain and more severe mental and physical health symptoms than noncombat injured personnel exposed to similar wartime stressors.[15-18] Veterans with comorbid symptoms have increased care utilization and almost double the costs of care within the Veterans Health Administration (VHA), a division of the U.S. Department of Veterans Affairs (VA), than those with chronic pain or PTSD alone.[19]

Early pain interventions in the combat theater, during transportation, and throughout acute care hospitalization improve pain outcomes[20-24] and potentially reduce the risk of developing mental health illnesses after combat injury.[25,26] Traumatic tissue damage inflicted by combat injuries, triggers an extensive inflammatory reaction consisting of the release of neurotransmitters to elicit an intracellular and neuropsychological response.[27] When undermanaged, this persistent inflammatory response can lead to chronic pain. The initial management of acute pain may benefit injured persons by interrupting this cascade of neurotransmitters.[28] This interruption may mitigate the development of chronic pain and thereby limit the interactions between pain intensity and PTSD symptom severity that can contribute to disability.[29] Comprehensive pain management, delivered as close as possible to the time of injury, is essential for all seriously injured persons. Despite robust research in the field of analgesics used after combat injury for improving pain management, the mechanisms of optimal delivery of anesthesia and analgesia after serious injury remains under researched.[30,31] Since most who sustain serious injuries will

survive, it is critical to ensure that injured service members have every opportunity to return home with minimal pain.

Purpose and Outline of the Research

This chapter is a brief overview of the dissertation and contextualizes this research. The purpose of this work is to identify the complex interrelatedness of pain and mental health conditions, such as PTSD, and the reciprocal influence symptoms have after combat injury. Additionally, this work evaluates the effects of early pain management after combat related-injury on pain intensity and interference. The chapter provides a brief summary and rationale of terms used throughout the dissertation. The intervention of interest, regional anesthesia (RA), is introduced and its utility in addressing the pain management challenges of combat-injured persons is discussed. An overview of the aims of each chapter follows before considering the significance of this work.

Subsequent chapters include the three component papers that comprise this dissertation. Initially, an integrative review of the extant literature was undertaken in order to identify clinical presentations and relationships between PTSD, depression, and pain after injury among OEF/OIF military personnel and veterans (Chapter 2). The remaining chapters detail a secondary analysis of the longitudinal data from the Regional Anesthesia Military Battlefield Pain Outcomes Study (RAMBPOS) (Chapters 3 and 4). Finally, the dissertation concludes with a discussion on leveraging the findings of this symptom science research to inform future pain management approaches in order to improve short- and long-term health outcomes after serious injury (Chapter 5).

RAMBPOS is a prospective longitudinal cohort study investigating the effects of early aggressive RA following major combat-related limb injuries on subsequent pain, functional status, behavioral health, and health related quality of life outcomes.[32] Individuals received RA either in a combat support hospital, during evacuation transportation, upon arrival to a U.S. military medical facility, intraoperatively, or throughout acute care. Individuals not receiving RA within two months of injury received conventional systemic pain management. Military personnel hospitalized with at least one major limb combat-related injury between 2007 and 2014 were eligible for enrollment during acute care or inpatient physical rehabilitation at one of two domestic U.S. military treatment facilities. Participants were excluded if they sustained major head trauma with cognitive deficits, defined as moderate or severe traumatic brain injury (TBI), had an inability to concentrate, clinician observed poor judgment and impulse control, substantial hearing loss, and individuals with bilateral upper extremity amputation with no alternate means to complete survey forms. Exclusion criteria were implemented due to potential cognitive inability to provide patient-reported outcomes.

The final sample of 386 combat-injured participants provided sociodemographic, pain, behavioral health, and injury data. After being screened and enrolled during acute care or rehabilitation, participants could join RAMBPOS anytime within two years after injury. Over the telephone, patient-reported outcomes were collected monthly in the first six months after injury and every three months thereafter, up to two years post-injury (See study schema in **Figure 1-1**). Retrospective abstraction of injury and clinical care data from health records during the initial hospitalization at military facilities were

integrated into the dataset, including pertinent injury information, receipt of early RA, and other multimodal pain therapies. The study was an interdisciplinary partnership between providers and researchers at Walter Reed National Military Medical Center, Brooke Army Medical Center, Veterans Affairs Office of Research and Development, Defense & Veterans Center for Integrative Pain Management, and the University of Pennsylvania.

Definition of Terms

Polytrauma

Due to the proliferation of high velocity weapons and IEDs employed in modern warfare, it is important to examine the complex injury patterns and mechanisms sustained by U.S. military personnel in Iraq and Afghanistan. Polytrauma is defined as injuries to multiple organ systems and anatomical regions of the body, most often due to blast exposure. Polytrauma comprises internal bleeding, major extremity injuries, TBIs, and other neurological injuries.[5] Nearly three quarters of all combat casualties in OEF/OIF are the result of explosive mechanisms.[3] These intense explosive reactions catalyze a pressurized blast wave that cause compression and shearing of tissue, damage to gas-filled organs (e.g. lungs), and TBI. Subsequent injuries after a blast, include blunt or penetrating injuries as materials from within a bomb casing and environmental debris are carried with the explosion.[33] All participants in RAMBPOS experienced at least one major limb injury and sustained a mild TBI (mTBI) given the mechanisms of their injuries. For the purpose of this dissertation, polytrauma is inclusive of major limb injuries, and severe or serious injuries.

Pain

Pain is an expected response to severe injury. Pain is defined as "the unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage".[35] The tissue damage induced by severe physical trauma initiates an inflammatory response of neurotransmitters that heightens both peripheral and central nervous system sensitization. Prolonged activation of this inflammatory response and nociception can cause a reduction in pain thresholds, allodynia, and an increased reaction to noxious stimuli, hyperalgesia.[36] These processes ultimately lead to maladaptive neuroplasticity, the remodeling of neuronal structures that can contribute to the transition from acute pain response to chronic pain.[27] Chronic pain is pain that persists beyond the expected time of healing; three months is the most often used point of division between acute and chronic pain.[35] About 60% of severely injured civilians experience injury-related pain a year after trauma care.[37] In comparison, over 80% of combat-injured veterans report experiencing chronic pain between 6 to 8 months after injury.[10,12]

Pain is a multidimensional phenomenon, requiring several levels of measurement in order to accurately capture an individual's painful experience.[29,38] Subjective pain intensity is a common measure in clinical practice and research. Pain intensity is defined as the severity to which pain is experienced. Common assessments of pain intensity include numeric rating scales where zero (0) refers to no pain, and ten (10) is the greatest severity, or most intense, pain can be experienced. However, pain is an inherently subjective experience and individuals interpret measurement scales differently. As such,

it is imperative pain intensity be evaluated beyond just what a research participant or patient is currently experiencing at time of assessment.[39] Measuring different components of pain, such as worst pain or least pain experienced in the past 24 hours, can provide valuable insight between assessment points in prospective research. Measuring the multiple dimensions of pain, such as worst, least, and current pain, is important to capturing patient's total pain experience. Pain interference is defined as the impact of pain on daily living and functioning.[40,41] The extent of pain interference refers to how pain hinders a person's engagement with social, cognitive, emotional, physical, and recreational activities. When measured and discussed together, in this research, pain intensity and interference are referred to as patient-reported pain outcomes, or simply pain outcomes.

Post-traumatic Stress Disorder (PTSD)

PTSD is a mental health condition that can develop after experiencing a traumatic and/or dangerous event, such as combat injury. Physical trauma can cause a dysregulation of multiple biological stress-mediating systems.[42] While individuals' responses to trauma differ, it is common to experience symptoms of post-traumatic stress (PTS). To be diagnosed with PTSD, an individual needs to present with one re-experiencing symptom (e.g. nightmares, flashbacks), three avoidance symptoms (e.g. loss of interest, amnesia, social detachment), and two hyperarousal or reactivity-related symptoms (e.g. difficulty sleeping, hypervigilance) out of 17 qualifying PTS symptoms for at least one month that impairs an area of their functioning, according to the American Psychiatric Association's 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).[43]

Not all combat-injured individuals will develop PTSD. On average, 11% to 20% of OIF/OEF veterans have a PTSD diagnosis in a given year;[44] with a higher proportion, between 30% to 68%, observed in combat-injured veterans.[9,12,14] For the purpose of this dissertation the term PTSD (DSM-IV criteria) will be used throughout when referring to both PTSD and PTS. The Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition (DSM-5) was published after RAMBPOS screening and enrollment was completed. Therefore, the DSM-IV criteria for PTSD were utilized to ensure continuity throughout the study period across participants.

Symptom Trajectories

Symptom trajectories, as defined in this dissertation, are changes in a disease's or a condition's clinical presentation over time. Evaluating symptom trajectories is essential to identifying interceding points when effective interventions, capable of altering the course of symptoms, can be used in clinical practice. Moreover, investigations of disease specific symptom trajectories can enable the identification of pathways that change the severity of co-occurring symptoms, or symptom clusters, and inform best strategies for managing conditions simultaneously. Due to the frequent co-presentation of both pain and PTSD in veterans (50% to 80% of veterans diagnosed with PTSD report experiencing chronic pain),[9,12,46] it is of value to consider the potential influence symptom trajectories have on one another.

Pain after injury is dynamic and requires longitudinal assessment by clinicians and researchers. Pain trajectories offer valuable insight into understanding clinical presentations of pain after combat injury.[47] Current evaluations of post-combat injury

pain are predominantly cross-sectional[21,24,48] and divided between understanding acute pain or chronic pain presentations.[18,22,26] Previous investigations on acute postoperative pain demonstrate the utility in capturing pain trajectories.[47,49] For example, there is mixed evidence to support that acute pain trajectories, specifically individuals with high pain intensity, can predict the development of post-surgical chronic pain several months later.[50] There is a value to understanding acute pain trajectories given that they provide greater information of change in pain intensity over time than conventional intermittent assessments, while also improving measurement precision.[47,49,51] Since pain intensity is subjective, it is necessary to assess intra-individual fluctuations in response to acute pain interventions and chronic pain prevention strategies.[52] Considering pain trajectories are dynamic in nature, simple linear modeling may be inadequate to other statistical approaches, such as mixed effects modeling[47] or probabilistic Markov modeling.[53] Markov modeling has been demonstrated to be a feasible method for simulating disease processes, including postoperative pain trajectories,[53] but has yet to be applied in characterizing post-combat injury pain trajectories. Markov modeling allows for the creation of pain states, defined as a quantified measure of pain intensity at a discrete time point in recovery after injury. The transition from one pain state to another (i.e. fluctuations in pain intensity) over time, can be considered a trajectory.

PTSD symptoms also have a variable course after traumatic events that can be acute or chronic, with symptoms fluctuating, remitting, or even worsening.[44,54] Therefore, capturing PTSD symptom trajectories after injury are of vital importance in order to inform care throughout recovery. The majority of studies following trauma exposed

persons, often do not exceed one year of evaluation and do not include more than two assessment points.[55] However, a few of the longitudinal investigations that do exist highlight the diverse presentations of PTSD symptom trajectories, and that subsyndromal levels of PTSD can contribute to disability and inhibit recovery.[56] This sub-threshold PTSD symptom severity is the most common trajectory seen in OEF/OIF military personnel and veterans.[57] However, more research is required to examine distal health outcomes predicted by PTSD symptom trajectories.[58]

Regional Anesthesia (RA)

Early pain management interventions, including RA, are paramount in the immediate post-traumatic injury period and throughout acute care hospitalization. RA is an effective and efficient intervention to manage acute pain and improve pain outcomes.[24,48,59-61] When used as part of a multimodal regimen, RA can target discrete components of the peripheral and central pain pathways to provide effective analgesia at lower opioid dosing and producing fewer adverse effects than standard systemic anesthesia and analgesic approaches.[62] Multimodal analgesia refers to the combination of analgesic drugs from different classes that have a synergistic effect and can maximize reductions in pain intensity at lower doses and reduced dependence on opioids.[62] RA delivered in RAMBPOS includes the use of neuraxial anesthesia, the local administration of an anesthetic into the spinal cord's epidural or intrathecal space, as well as peripheral nerve blocks, directed towards an isolated nerve or plexus through the injection of a local anesthetic under ultrasound guidance. These RA techniques allow for a high precision delivery of analgesia to injured areas of the body to augment multimodal regimens.

The austere environment, combined with the complex care associated with combat trauma, necessitates the use of agile and effective pain management interventions. For example, systemic pain therapies come with challenges, including timeliness of administration and therapeutic effect.[62] General anesthesia requires advanced logistics, such as availability of a dependable source of electricity and compressed gas that are not always available in the battlefield. Use of RA, is hypothesized to reduce complications in civilian surgical patients.[62-65] Improved outcomes with RA, over systemic approaches, include the avoidance of intubation and mechanical ventilation, minimal risk of respiratory and circulatory depression, and improved postoperative analgesia.[31,65] After being introduced in the Vietnam War, RA is now commonly used to manage pain following injuries in both Iraq and Afghanistan. In military and the civilian populations RA has proven benefits of optimal acute pain severity control with fewer side effects, minimal or non-opiate therapy, and improved functional recovery.[26,31,59,65-67] A meta-analysis comparing RA to conventional analgesia (e.g. intermittent opioids) found RA to be effective in preventing persistent postoperative pain, a type of chronic pain, in civilian populations up to one year after surgery.[68] Yet, this analysis did not include studies with combat-injured OEF/OIF military personnel, and results were weakened due to both small samples and the limited availability of data beyond one year. A cross-sectional study of OEF/OIF amputees identified individuals who received pain management through RA had over 50% lower odds of developing subtypes of chronic pain, than amputees not receiving RA.[69]

Chapter Aims and Rationale

The following chapter aims were designed to achieve the goals this dissertation, which were to identify the complex interrelatedness of pain and mental health, and the effects of RA on patient-reported outcomes after combat related-injury.

Chapter 2

Aim: This integrative review synthesized clinical presentations and interrelationships among characteristics and mechanisms of combat injury, PTSD, depression and pain in American military service members and veterans serving in OEF/OIF wars. This paper provides an evidence table of clinical presentations of these often co-occurring conditions and injury characteristics that helps to contextualize the RAMBPOS participants. The results of this review are foundational to understanding combat trauma for the data-based papers that follow.

Rationale: The interrelationships and presentations identified in this review of the literature establish a clinical knowledge base for this dissertation and future lines of inquiry in the field of combat injury science. This essential review of the literature is one of the first to examine the polytrauma phenomenon from the nursing science perspective.

Chapter 3

Aim: Evaluate the association of RA and PTSD symptom trajectories, on pain intensity and interference over the first two years after injury.

Hypothesis: There will be a positive moderate correlation between pain intensity and interference, and PTSD symptom severity using repeated patient-reported outcome

measures. Pain intensity and interference point estimates will differ based on RA receipt status, and on PTSD symptom trajectories throughout the course of RAMBPOS.

Rationale: This analysis of the RAMBPOS cohort is critical to understanding the effects of PTSD symptom trajectories on pain following combat injury. Moreover, it is imperative to utilize the possible relationship between PTSD trajectories and pain outcomes as support for the value of integrating simultaneous care of either condition across rehabilitation and recovery.

Chapter 4

Aim: Characterize probabilistic pain trajectories, stratified by those who did or did not receive RA, after combat injury across multiple dimensions of pain intensity.

Hypothesis: Using a Markov model approach to examine pain trajectories, will illustrate that participants receiving RA are less likely to transition to and less likely to remain in a high pain intensity state over the two year model period compared to those not receiving RA.

Rationale: By using patient-reported pain outcome measures to characterize pain trajectories, it is possible to capture the multidimensional nature of pain after combat injury while accounting for both time and pain management interventions. The construction of probabilistic pain trajectories using transition matrices, stratified by RA recipients, goes beyond simple linear numeric scales assessing temporal cross-sectional pain experiences and captures the depth of pain presentations experienced after combat injury.

With the parent study's data, this dissertation is an opportunity to understand the association of pain and PTSD after injury, and consider the long-term benefits of receiving early pain management through RA. The original aims of this dissertation are unique from that of RAMBPOS, which only examined pain outcomes between individuals who did or did not receive RA and did not consider mental health outcomes or symptom trajectories. The aims of this dissertation and research protocol received institutional review board (IRB) exempt status by the VA Medical Center Research & Development Committee (Protocol #01685) and the University of Pennsylvania (Protocol #827892).

This program of research is guided by The Biopsychosocial Model of Chronic Pain (**Figure 1-2**).[71] This model assumes the causes of, and health outcomes from, chronic pain are affected by a magnitude of diverse social, physical, pathological, environmental, and psychological factors in an individual's life. Therefore, in order to adequately manage chronic pain, all of these factors must be addressed by providers and caregivers to the fullest extent possible. In this research, the model is used to place an injured individual's perception and response to pain in the context of the interrelationships between biological changes from tissue trauma and psychological health, such as PTSD.[72] There is a shared pathophysiology between comorbid chronic pain and PTSD that can be amplified when dysregulation in the peripheral processes (i.e. immune, autonomic, endocrine) occurs in response to tissue trauma.[73] Stress stimulated from traumatic events, such as injury, increases dysregulation in the periphery processes that heighten afferent feedback to the central processes in the model. For example, PTSD

associated neurotransmitters released from the inflammatory immune response go on to potentially influence pain transmission and amplification along these pathways. Behavioral reactions that result from changes in the central cognitive processes may influence PTSD symptom presentations, alter patient-reported pain interference, and exacerbate emotional responses. Pain driven emotions, such as feelings of vulnerability or anger, that are also associated with PTSD interact and alter cognitive appraisals of pain. Cognitions, in turn, attach meaning to the emotional experience and may activate emotional responses and amplify the pain experience, propagating a cycle of nociception, distress, and disability due to comorbid pain and PTSD.[71,72,74] The social aspects of a combat-injured individual's life interact with both the physiological and psychological aspects of injury to further modulate symptom severity. The severity of symptoms can then perpetuate an injured-person's ability to meet social and interpersonal relationship expectations, independently complete activities of daily living, and navigate their environment effectively. By adapting Engel's generic biopsychosocial model of disease,[75] pain scientists have used the Biopsychosocial Model of Chronic Pain to identify that:

> "Research supports a strong bidirectional link between mood disorders and persistent pain; the development of an enduring pain condition confers a substantially increased risk for the subsequent diagnosis of an affective disorder, and psychosocial variables such as depression, anxiety, and distress are among the most potent and robust predictors of the transition from acute to chronic pain…efficacious analgesic treatments that reduce the frequency and intensity of pain should have a beneficial effect on patients' affective states and appropriate treatment of emotional distress should have a positive influence on the experience of pain."[76]

However, in order to understand the development, co-occurrence, and contiunuation of PTSD symptoms and pain requires this area of research to move beyond cross-sectional

descriptions of symptoms after injury. Further, research examining both conditions must consider the effects of analgesic treatments, which can influence various aspects of the biopsychosocial model in the efferent and afferent feedback between peripheral and central processes. To do so requires the assessment of larger datasets measuring these interrelated conditions, in order to further illuminate their interactions on one another. For this reason, components of this dissertation consider how PTSD trajectories influence pain intensity and interference, while also evaluating the effects of RA, which in turn may improve acute pain and potentially influence the development of future chronic pain.

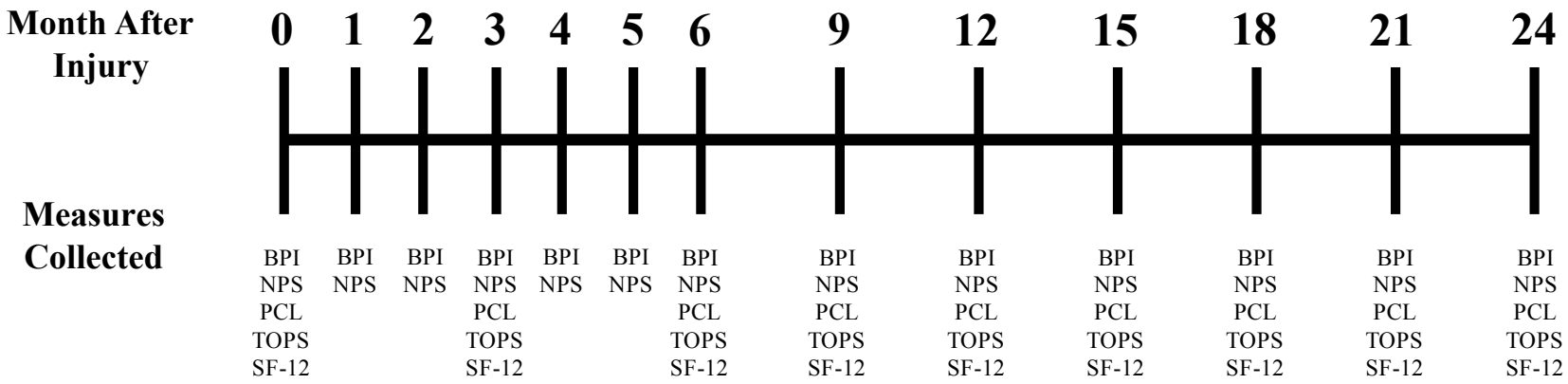
Significance

The ability to expand science in the use of early acute pain management with RA and demonstrate its association with long-term health outcomes will be invaluable for future trauma responders and clinicians managing acute pain after injury. The delivery of RA after injury requires a coordinated effort among emergency responders, surgeons, nurses, and trained anesthesia providers, such as Certified Registered Nurse Anesthetists (CRNA).[20,62] CRNAs are present in military, veteran, and civilian healthcare settings, and therefore it is critical that CRNAs are trained to deliver effective pain management and trauma care to the fullest extent of their scope of education and practice.[77] Additionally, timely and effective pain management is paramount to civilian, military, and veteran populations. Studying short- and long-term benefits of early RA for combat trauma in this dissertation has the potential to strengthen injury science and provide foundational support to implementing CRNA led interventions after injury.

Understanding the short- and long-term health outcomes following serious injury is a priority to both military and civilian agencies. This dissertation directly supports the missions of many national organizations and their commitments to meeting the health needs of the nation's injured service members and civilians. The objectives of this dissertation are well positioned with the National Institute of Nursing Research's (NINR) Strategic Plan to better manage symptoms of acute and chronic illnesses such as pain.[78] NINR's longstanding commitment to recognizing that pain can be a debilitating symptom and chronic condition, furthers the significance in developing and testing effective CRNA led pain management interventions, like RA. Similarly, the 2011 Institute of Medicine, now known as the National Academy of Medicine, report called for a cultural transformation in pain prevention, care, and research to be guided by the National Institutes of Health led National Pain Strategy.[79] The National Pain Strategy seeks to promote research that benefits citizens most at risk of developing chronic pain and promote the implementation of non-opiate interventions.[80] The use of comprehensive multimodal analgesics delivered via RA offers a low dosing, or opioid-sparing, alternative for managing pain after serious injury. Research evaluating the effects of RA, such as this dissertation, aligns with the 2016 Centers for Disease Control and Prevention Guideline for Prescribing Opioids for Chronic Pain's call for researchers to evaluate the effectiveness of alternative non-opiate treatment options for pain.[81] The findings of this dissertation will further the knowledge needed to leverage advances in RA techniques in order to promote best pain management practices, as put forth by the Army Surgeon General's 2010 Pain Management Task Force.[82]

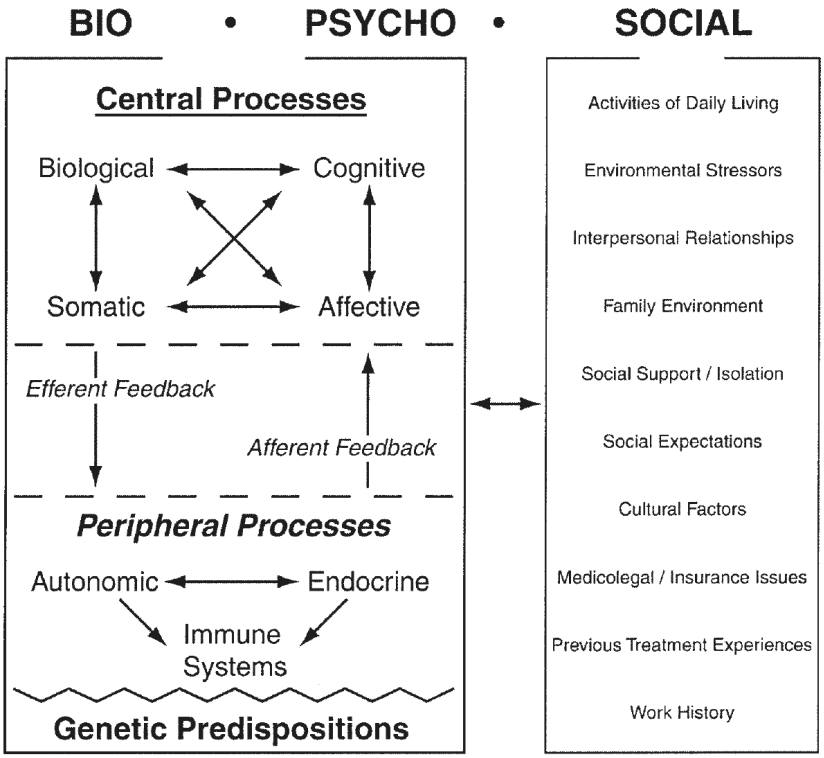
The health needs of combat injury survivors continue long after acute care, and therefore healthcare providers must anticipate and evaluate changes in symptoms. Findings from this dissertation emphasize that continued evaluation by clinicians and researchers is required in this population, based on the complex presentations between pain, PTSD, and depression after combat-related injury (Chapter 2). This dissertation evaluates the long-term effects of RA, and the reciprocal influence of PTSD total symptom severity trajectories, on patient-reported pain outcomes up to two years after injury (Chapter 3). Moreover, innovative methodologies can be utilized to identify which acute care interventions are most likely to be successful in changing the trajectory of acute to chronic illnesses, and how interventions can influence the dynamics of pain presentations (Chapter 4). Findings from this dissertation have the potential to inform future trauma care planning, beginning from the time of acute care, in order to optimize the health of traumatically injured persons throughout rehabilitation and recovery.

Figure 1-1 Regional Anesthesia Military Battlefield Pain Outcomes Study (RAMBPOS) Schema



BPI = Brief Pain Inventory; NPS = Neuropathic Pain Scale; PCL = PTSD Checklist; TOPS = Treatment Outcomes in Pain Survey; SF-12 = 12-item Short Form Survey.

Figure 1-2 The Biopsychosocial Model for Chronic Pain



A conceptual model of the psychosocial interactive processes involved in health and illness.
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CHAPTER 2

Complexity of the Relationships of Pain, Posttraumatic Stress, and Depression in Combat-Injured Populations: An Integrative Review to Inform Evidence-Based Practice[1]

Abstract

Background

Understanding the complex interrelationships between combat injuries, physical health, and mental health symptoms is critical to addressing the healthcare needs of wounded military personnel and veterans. The relationship between injury characteristics, pain, posttraumatic stress disorder (PTSD), and depression among combat-injured military personnel is unique to modern conflicts and understudied in the nursing literature.

Aim

This integrative review synthesizes clinical presentations and relationships of combat injury, PTSD, depression, and pain in Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) United States military service members and veterans.

Methods

A literature search was conducted using relative key terms across databases to identify peer-reviewed publications between 2001 and 2016 that examined health

[1]The chapter is the author's original work. A final version of this manuscript is published as NA Giordano, C Bader, TS Richmond, RC Polomano. *Worldviews Evid Based Nurs*, 2018;15:2,113–126. © 2018 Sigma Theta Tau International, Wiley Periodicals, Inc. No modifications are permitted without the permission of the copyright holder.

outcomes of combat-injured persons in OEF and OIF. The quality of evidence was evaluated and results synthesized to examine the association of combat injury as a risk factor for PTSD, the relationship of PTSD and depression pre- and postinjury, and pain management throughout care.

Results

Twenty-two articles were included in this review. Greater injury and pain severity poses risks for developing PTSD following combat injury, while early symptom management lessens risks for PTSD. Depression appears to be both a contributing risk factor to postinjury PTSD, as well as a comorbidity.

Linking Evidence to Action

Findings demonstrate a compelling need for improvements in standardized assessment of pain and mental health symptoms across transitions in care. This integrative review informs nurse researchers and providers of the clinical characteristics of pain, PTSD, and depression following combat injury and offers implications for future research promoting optimal surveillance of symptoms.

Introduction

Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) led to the deployment of millions of United States military personnel. Over 50,000 troops serving in OEF and OIF experienced combat injuries (Defense Casualty Analysis System, 2017). Mechanisms of battlefield trauma have shifted to high-velocity weapons and improvised explosive devices, capable of inflicting devastating injuries. Polytrauma describes injuries to multiple organ systems and anatomical regions of the body, often due to blast exposure. Polytrauma includes internal bleeding, major extremity injuries, traumatic brain injuries (TBI), and other neurological injuries (United States Department of Veterans Affairs, 2015). Advancements in military trauma care and evacuation capabilities to higher levels of care have led to unprecedented increases in survival rates and subsequently new patterns of complex healthcare needs of polytrauma survivors (Clifford et al., 2014).

The polytrauma clinical triad, defined by pain, posttraumatic stress disorder (PTSD), and TBI, is evident in over 40% of polytrauma OEF and OIF military service members and veterans (Lew et al., 2009). High rates of mental disorders, such as depression, coexist with this polytrauma clinical triad, further complicating the polytrauma rehabilitative services required to address biopsychosocial healthcare needs postinjury (Vyas et al., 2016). The concerning prevalence of depression seen in combat exposed uninjured veterans (28%), compared to other mental health conditions, emphasizes the importance of examining the interrelatedness of depression, PTSD, and pain after combat injury (Thomas et al., 2010). Further, there is evidence that assessment and management

of depressive symptoms, for all veterans, seeking care in primary care settings is an effective suicide prevention approach (Denneson, Williams, Kaplan, McFarland, & Dobscha, 2016).

This integrative review summarizes and analyzes the state-of-the-science pertaining to the complex relationships of pain, PTSD, and depression experienced by combat-injured OEF and OIF military service members and veterans. Because pain, PTSD, and depression are present in the U.S. civilian trauma population, research from combat-injured military service members and veterans can inform civilian trauma care (National Academies of Sciences, Engineering, and Medicine, 2016). Although TBI is part of the polytrauma triad, this review only focuses on research addressing pain and mental health outcomes associated with combat injuries, independent of neurological conditions. The polytrauma literature continues to expand, however, there is still a paucity of studies examining the interrelatedness of pain, PTSD, and depression associated with combat injury. The purpose of this review is to evaluate and synthesize current research on the influence of clinical injury characteristics related to the onset and persistence of pain, PTSD, and depression symptoms in military personnel and veterans seeking care across health settings.

Methods

Search Strategy

A targeted search of available literature, published between September 2001 and December 2016, was conducted in PubMed, CINAHL, Scopus, and EMBASE, using the following National Library of Medicine Medical Subject Headings terms and key words:

adult (PubMed defines as >19 years); military personnel; veterans; veterans' health; U.S. Department of Veterans Affairs; Veterans Hospitals; wounds, injuries; penetrating wounds; gunshot wounds; multiple trauma; pain; PTSD; and depression (Figure 2-1). Combat injury refers to a sustained injury incurred in the line of duty because of armed conflict (United States Department of Veterans Affairs, 2015). Search terms are available online with this article.

Data Extraction

Studies retained for analysis met the following criteria: (a) samples included U.S. military personnel or veterans who sustained combat injuries in the OEF and OIF wars; (b) pain, PTSD, and depression were primary or secondary outcomes; (c) investigations conducted in combat theater, military or Veterans Health Administration (VHA) healthcare facilities; and, (d) secondary analyses of Department of Defense (DoD) or VHA databases. Citations excluded were: (a) case studies, commentaries, expert consensus reports, and editorials; (b) investigations of military or veteran populations with TBI as a primary variable of interest; (c) studies not investigating combat-related physical trauma or an outcome of interest (e.g., pain, PTSD, depression); (d) publications prior to September 11, 2001; (e) non-English publications; and (f) investigations of biomarkers, genomics, or imaging. Of the 1,848 database citations, 1,778 abstracts met the criteria for inclusion, and 286 full text publications were evaluated applying exclusion criteria. Twenty-two studies were deemed acceptable for this review (Figure 2-1).

Data Analysis

Studies were evaluated for methodological quality, informational value, and representativeness of combat-injured military personnel and veterans (Whittemore & Knafl, 2005). The strength of evidence of each study was evaluated using Melnyk and Fineout-Overholt's (2011) "Rating System for the Hierarchy of Evidence" (Level 1—highest to Level 7—lowest). The strongest evidence to base clinical practice on is rated Level 1 and includes both systematic reviews and meta-analyses of randomized controlled trials. Level 2 refers to well-designed randomized control trials, whereas Level 3 evidence comes from controlled trials without randomization. Level 4 contains cohort and case-control research studies. Level 5 evidence refers to systematic reviews of descriptive and qualitative studies. Level 6 includes single descriptive studies and qualitative work, and Level 7 refers to expert opinions. The integrative review process included an analysis of samples across studies, data reduction, data display, data comparison, conclusion drawing, and verification throughout the Results section, with key findings synthesized and evidence rated in Table 2-1 (Whittemore & Knafl, 2005).

Results

The 22 studies included in this review were published in peer-reviewed journals and comprised 10 retrospective analyses, four prospective observational studies, four retrospective cohort studies, two cross-sectional descriptive studies, one descriptive observational study, and one mixed-methods study.

Samples, Data Sources, and Settings

Samples ranged from 50 to 191,747 participants in size, and were predominately young (22–31 years, average age), Caucasian (46–95% of samples), and almost entirely male (72–100% of samples). Sample data sources for retrospective studies were obtained from the Combat Trauma Registry Expeditionary Medical Encounter Database and the Joint Theater Trauma Registry, subsequently renamed DoD Trauma Registry, and National VHA health records. Other studies were conducted at, or using data from, military facilities (e.g., domestic and overseas, including a combat support hospital) and within the VHA system. Variations in study settings and data sources, from time of combat injury to rehabilitative care, provide a broad range of results capturing clinical presentations postinjury.

Combat Injury: Risk Factor for PTSD

The incidence of PTSD varied within study samples, from 4.2% to 44%. The studies in this integrative review utilized clinician diagnoses, both ICD-9 codes and medical records, as well as self-report measures, such as the PTSD patient checklist (PCL) scored using the diagnostic criteria based on Diagnostic and Statistical Manual IV-TR (DSM-IV). Combat injury was found to be a significant risk factor for developing PTSD. Baker et al. (2009) established that injury during combat was significantly related to a positive PTSD screening among combat-injured veterans compared to those without injuries (odds ratio [OR], 3.14; 95% confidence interval [CI] [1.73, 5.71]). Despite the cross-sectional approach and self-report of physical combat injury status, which resulted in a low quality of evidence (Level 6), Baker et al. provide support of the association between

injury status and PTSD. Using the PCL, Phillips, LeardMann, Gumbs, and Smith (2010) found that individuals who experienced gunshot wounds or serious injury in combat were more likely to develop postdeployment PTSD compared to those without similar trauma (OR, 3.51; 95% CI [1.58, 7.77]). Phillips et al. provide stronger support for this relationship (Level 4), largely due to the prospective nature of the study. In addition, higher injury severity scores (ISS) were identified as a key variable for developing PTSD among military personnel. Initial findings by MacGregor, Corson et al. (2009) and MacGregor, Shaffer et al. (2009) suggested that combat-injured military personnel experienced higher rates of PTSD compared to uninjured peers. MacGregor, Tang, Dougherty, and Galarneau (2013) found that after adjusting for ISS, those injured in combat were twice as likely to develop PTSD compared to noncombat-injured military personnel (OR, 2.10; 95% CI [1.60, 2.75]).

ISS is used to evaluate anatomic injury and severity ranging from 0 to 75, with 75 indicating the greatest severity of injuries (Baker, O'Neill, Haddon, & Long, 1974). Combat-injured military personnel with, what MacGregor et al. (2013) defined as, an ISS of moderate (4–8) and serious-severe (9+) had significantly increased odds of developing PTSD (OR, 1.49; 95% CI [1.11, 2.00]) compared to those with mild (1–3) ISS (OR, 1.64; 95% CI [1.01, 2.68]). Prior combat injury was also predictive of PTSD (OR, 1.96; 95% CI [1.22, 3.16]). Sandweiss et al. (2011) recognized that within the Millennium Cohort combat-injured population, a 3-unit increase in ISS translated to 16% increased likelihood of developing postdeployment PTSD symptoms (OR, 1.16; 95% CI [1.01, 1.34]). This

summates to a clear connection between combat injury, injury severity, and subsequent development of PTSD, relative to noncombat-injured military personnel.

Researchers identified an association between injury mechanism and PTSD. Investigators at a polytrauma rehabilitation center observed veterans with combat blast-related injuries had significantly higher rates of PTSD (45.1% of sample) compared to those with noncombat-related injuries (2.1%) or injuries without blast exposure (11.8%, $p < .001$; Clark, Walker, Gironda, & Scholten, 2009). McLay, Webb-Murphy, Hammer, Volkert, and Klam (2012) reported veterans experiencing both blunt and penetrating combat injuries, had significantly higher rates of PTSD symptoms compared to those with no injuries or solely penetrating trauma ($p < .05$). In addition, Mora et al. (2009), identified that within their sample of burned combat-injured military personnel, individuals exposed to blast were more likely to screen positive for PTSD than those without blast injuries (OR, 3.27; 95% CI [1.17, 9.16]). This sample of severely burned military personnel exhibits that PTSD symptoms can potentially be a function of type, severity, and mechanism of injury. The increased odds of PTSD, from combat injury, further compounded by severity, indicates polytrauma may influence mental health outcomes. Not all studies included in this review measured PTSD severity, and many only reported the presence of PTSD, which limited the ability to examine severity of PTSD with injury severity.

Depression and PTSD

Depression rates within studies targeted for this review ranged from 7% to 27%, and were measured using self-reported measures or ICD-9 codes. The coexistence of PTSD

and depression in combat-injured service members is complex, and some researchers contend that previous mental health diagnoses act as precursors to the development of PTSD. Sandweiss et al. (2011) identified that a preinjury mental disorder, including depression, was a risk factor for developing PTSD. Researchers screening for PTSD symptoms found those with one or more mental disorder at baseline had 2.52 times (95% CI [2.01, 3.16]) greater risk for postdeployment PTSD after injury. The prospective approach, employed by Sandweiss et al., provides a unique opportunity to examine depression prior to injury and offers strong evidence to support this predisposing relationship (Level 4). Similarly, MacGregor et al. (2013) documented that a mental health diagnosis within 1 year prior to deployment increased odds of developing PTSD following injury (OR, 2.69; 95% CI [1.50, 4.81]; Level 4).

Although the aforementioned studies support a higher likelihood for PTSD with an existing mental disorder prior to combat injury, others purport that there is a bidirectional relationship between PTSD and depression. Several researchers identify depression as being a common mental disorder appearing with PTSD following trauma. Clark, Bair, Buckenmaier, Gironda, and Walker (2007) found PTSD evident in 44% and depressive disorders in 24% of their sample. Researchers following combat-injured military personnel transitioning from DoD to VHA care reported similar rates, for PTSD (38%) and depression (27%; Copeland et al., 2011). Similar work by Clark et al. (2009) identified elevated rates of PTSD and depression among polytrauma care seeking veterans who experienced combat blast related injuries (45.1%, 25.5%, respectively) compared to their noncombat-injured (2.3%, 7.0%) and combat-injured without blast

exposure (11.8%, 14.7%). VHA researchers report that in a sample of veterans, those injured in combat with a PTSD diagnosis were significantly more likely to also meet depression criteria compared to those uninjured ($p < .001$; Baker et al., 2009). However, the relationship, whether causal-effect or bidirectional, could not be determined due to the cross-sectional nature of these studies (Level 6). Within a national sample of OEF and OIF veterans seeking care, Pugh et al. (2014) identified that depression was a significant comorbidity with PTSD for polytrauma veterans. Veterans presenting with "comorbidity clusters," defined by the presence of polytrauma, PTSD, and depression were most likely to have adverse outcomes, as evidenced by the high likelihood of emergency care, compared to individuals in "comorbidity clusters" without both PTSD and depression (OR, 3.90; 95% CI [3.70, 4.10]). Pugh et al. (2014) claim that depression is a central comorbidity that contributes substantially to healthcare utilization and adverse outcomes for veterans. Pugh et al.'s large sample size (N = 191,797) strengthens support for this relationship (Level 4); however, this study fails to account for time since injury or symptom severity.

The presence of PTSD and depression across VHA facilities, among combat-injured service members, demonstrates a need to investigate the interplay these two illnesses have on long-term health outcomes. Grieger et al. (2006) showed that early significant somatic symptom severity from combat injuries, as measured by the self-reported 15-item Patient Health Questionnaire, was associated with PTSD and depression diagnoses 7 months postinjury. In a combat-injured cohort, individuals with high somatic symptom scores (≥8, 0–26 scale) 1 month after combat injury had higher rates of mental health

diagnoses when compared to their less symptomatic peers (<8). Individuals with higher somatic symptom severity 1 month after injury were more likely to develop PTSD (OR, 9.10; 95% CI [4.10, 20.10]) and depression (OR, 5.70; 95% CI [2.40, 13.20]) 7 months later. These prospective findings by Grieger et al. provide evidence (Level 4) to support that initial symptom severity can potentially predict the development of mental health symptoms.

Pain and PTSD

Researchers examined pain severity, both immediately postinjury and throughout rehabilitation, and the potential role of pain management interventions in the development of PTSD. Holbrook, Galarneau, Dye, Quinn, and Dougherty (2010) established that morphine-based pain management, immediately following combat injuries, exerted a protective effect on the development of PTSD up to 2 years postinjury (OR, 0.47; 95% CI [0.34, 0.66]). Melcer et al. (2014) confirm the success of early pain management with morphine, over other medications, in reducing odds of developing PTSD up to 4 years after injury (OR, 0.40; 95% CI [0.17, 0.94]). Further, McGhee, Maani, Garza, Gaylord, and Black (2008) and McGhee et al. (2014) reported a lower prevalence of PTSD among injured service members who received ketamine during their surgeries compared to those who did not ($p = .044$). Findings from Buckenmaier et al. (2009) show early benefits of aggressive pain management include the reduced symptoms of anxiety and distress correlating with pain relief. These studies provide evidence for early effective pain control to reduce the development of PTSD and reduce early symptom severity.

Investigators evaluated pain and mental health symptoms long after initial injury. Stratton et al. (2014) revealed that baseline pain severity accurately predicted latent PTSD diagnoses, and PTSD severity predicted pain severity at 1-year follow-up ($\chi 2 = 3.66$; $p < .05$). This prospective study design offers evidence to support this association (Level 4). In polytrauma rehabilitative centers, researchers identified pervasive needs for the treatment of co-occurring pain and stress disorders, such as PTSD (Clark et al., 2007, 2009; Sayer et al., 2009). Pugh et al.'s (2014) analysis of "comorbidity clusters" concluded that pain demonstrated no consistent pattern in predicting adverse outcomes, unless comorbid with depression and PTSD. Individuals with all three comorbidities had the highest odds of adverse outcomes, such as homelessness (OR, 6.60; 95% CI [5.80, 7.50]) and suicide-related behaviors (OR, 13.30; 95% CI [10.30, 17.20]) than other polytrauma cohorts. Adequate pain management after injury potentially influences PTSD symptoms across healthcare settings.

Discussion

This integrative review examines the complex relationship between pain, PTSD, and depression, seen in combat-injured OEF and OIF military personnel. Findings underscore the importance of assessing for potential comorbidities after combat injury. The post-September 11, 2001 veteran population is projected to increase 46% by 2019, and while the VHA cares for millions of veterans, almost half seek care in civilian healthcare facilities (National Center for Veterans Analysis and Statistics, 2016). Nurses practicing in military healthcare facilities encounter service members and veterans injured in OEF and OIF. Because these nurses deliver care across all transitions of care from Level 1, at

the point of injury, to Level 5, at U.S. major military facilities, it is critical that they understand the consequences of combat injuries on physical and mental health (Bagg, Covey, & Powell, 2006). VHA and civilian nurses are also likely to care for veterans who sustained combat trauma, and they too must combine scientific knowledge, interdisciplinary collaboration, and patient and family advocacy to improve patient outcomes. Early recognition of trauma-related pain, PTSD, and depression, and interventions aimed at reducing their severity are essential to combat casualty and trauma care. Nurse Practitioners and Certified Registered Nurse Anesthetists are also practicing in military, veteran, and civilian trauma care settings and are positioned to assume responsibilities for the management of combat-injury related pain (Schoneboom et al., 2016).

Mental Health

There is an established association between combat exposure and mental health, particularly PTSD (Hoge, Riviere, Wilk, Herrell, & Weathers, 2014). However, the causal relationship between combat injury and subsequent development of PTSD is not clear. Numerous factors contribute to the preinjury, acute injury, and postinjury stages that can influence the development of PTSD among combat-injured military personnel. Several studies demonstrate the need to screen and identify predeployment risk factors, such as mental disorders and previous traumatic exposures. Researchers identified associations between injury severity (Baker et al., 2009; MacGregor, Corson et al., 2009; MacGregor, Shaffer et al., 2009; MacGregor et al., 2013; Sandweiss et al., 2011) and pain management in developing PTSD postinjury (Holbrook et al., 2010; McGhee et al.,

2008; McGhee et al., 2014; Melcer et al., 2014). Mechanistic type of injury, particularly blast or in combination with blunt and penetrating trauma, can influence the development of postinjury mental health symptoms (e.g., PTSD and depression; Clark et al., 2009; McLay et al., 2012; Mora et al., 2009; Pugh et al., 2014). Risk of developing PTSD is higher in those experiencing combat-related trauma, compared to individuals with noncombat-related injuries, and risk increases with injury severity (MacGregor, Corson et al., 2009; MacGregor, Shaffer et al., 2009; Sandweiss et al., 2011).

Several studies address the presence of depression preceding combat injury and subsequent development of PTSD (Clark et al., 2007; MacGregor et al., 2013; Sandweiss et al., 2011). Others described comorbid depression and PTSD following injury (Clark et al., 2009; Grieger et al., 2006). In civilian populations, individuals with comorbid PTSD and depression may experience more severe depression, increased healthcare cost, and lower physical functioning than individuals with either condition alone (Campbell et al., 2007). The foundation of research examining PTSD and depression symptoms as comorbidities highlights the need for further analysis of these relationships in combat-injured populations.

Pain in the Context of Combat Injury Care

Pain is one of the most frequently reported symptoms after combat injury. Pain management, in addition to alleviating postinjury acute pain, can reduce symptom severity of other physical and mental symptoms caused by trauma (Clark et al., 2007). Acute pain can be substantial when considering the extent of injury polytrauma entails. Moreover, combat-injured veterans may experience chronic pain. Chronic pain may

cause irritability, social withdrawal, depressed mood, sleep changes, and lead to disruption in social relationships (Katz & Rothenberg, 2005). VHA investigators report over one third of polytrauma survivors experience multiple types of chronic pain (e.g., neuropathic, phantom limb), and over two thirds of combat-injured veterans need pain management interventions throughout polytrauma rehabilitation (Clark et al., 2007, 2009; Copeland et al., 2011; Sayer et al., 2009). The prevalence of chronic pain and continued pain management needs in this population further emphasizes the urgency for early acute pain management.

Early pain interventions may mitigate the lasting effects of acute trauma that lead to the development of chronic pain by interrupting the cascade of events triggering neurotransmitter release, intracellular responses, and neuropsychological response. For example, Buckenmaier et al. (2009) and Buckenmaier, Mahoney, Anton, Kwon, and Polomano (2012) found that incorporating aggressive multimodal regional analgesia after injury significantly reduced pain intensity in combat-injured soldiers compared to soldiers receiving standard pain management. Clinical characteristics of injury (e.g., severity and mechanism) are associated with the risk of developing postinjury PTSD and depression (Grieger et al., 2006), as well as acute and chronic pain. A significant, but weak, relationship exists between ISS and acute pain severity (Fowler et al., 2011), and injury type (e.g., blast), which may interfere with pain relief (Clark et al., 2009). Given the disabling effects of undermanaged mental health conditions and comorbid chronic pain, early assessment and management of polytrauma related symptoms are critical. A previous study documents that injured OEF and OIF veterans with comorbid PTSD and

chronic pain experienced greater pain-related disability than veterans with chronic pain alone. However, the study sample did not include combat-injured veterans. OEF and OIF veterans with comorbid PTSD and chronic pain experienced greater pain-related disability than veterans with chronic pain alone (Outcalt et al., 2015). Unlike previous polytrauma reviews (Dobscha et al., 2009), this review highlights the multidimensional clinical presentations of pain in relation to depression and PTSD.

Limitations

There are limitations to the research included in this review. First, the literature has no unified means of measuring PTSD, depression, and pain postinjury, or even injury itself. Researchers utilized the ISS, however many relied on self-reported injury status. PTSD screening tools varied, with some using clinician diagnoses and others patient self-reports. Updated PTSD diagnostic criteria in the DSM-5 may limit the ability to understand the predictive factors leading to positive screenings of PTSD among military populations. However, researchers have demonstrated the consistency between DSM-IV and DSM-5 criteria within U.S. veterans (Miller et al., 2013). This affirms a consistency, at least in veteran populations, for PTSD assessments and the ability to compare previous studies to future work. Second, study designs affect overall generalizability and quality of findings. The few prospective studies and numerous retrospective studies, which the applied criteria consider to be of lower evidence quality, speak to the difficulties in conducting research investigating combat-injured populations. The inherent limitations of retrospective studies hinder the ability to identify causal relationships. Finally, small sample sizes and high attrition rates limit the ability to draw definitive conclusions about

the care of all combat-injured persons. For instance, Grieger et al. (2006) and Stratton et al. (2014) experienced attrition rates of 40% and 47%, respectively. This review demonstrates the necessity of understanding risk factors that complicate the relationship between pain and mental health, postinjury.

Future Directions

Improved survival rates after polytrauma warrant a need for more prospective longitudinal studies to capture these unprecedented symptom trajectories. The inclusion of comprehensive standard assessment measures is vital to optimizing the care of combat-injured persons and determining predictors of long-term health outcomes. Currently, initial trauma measures are valuable clinical tools, but not comprehensive to understanding long-term symptom trajectories. Several articles identified the value initial traumas measures, specifically ISS, can have in identifying individuals at risk of developing PTSD, however, civilian researchers have found that increasing objective injury severity is not directly related to the development of PTSD (Richmond et al., 2011). The integration of uniform health screening metrics in the recent Pain Assessment Screening Tool and Outcomes Registry (PASTOR), developed by the Pain Management Task Force, addresses the use of standardized measures for research and clinical care (Cook, Buckenmaier, & Gershon, 2014). PASTOR incorporates the National Institutes of Health's Patient-Reported Outcomes Measurement Information System (PROMIS®) Measures. For example, the Defense and Veterans Pain Rating Scale (DVPRS) has already undergone testing in military and VHA facilities (Polomano et al., 2016). PASTOR provides much-needed standardization of patient-reported outcome measures

for assessment across all transitions of care, phases of recovery, and reintegration into civilian life. Nurses are in a unique position to implement assessment measures and incorporate standardized measures in their clinical and research practices.

Conclusions

This integrative review examined the complex clinical presentations and interrelationships of pain, PTSD, and depression experienced by combat-injured military personnel and veterans. Injury severity is a contributing factor to the development of PTSD following combat injury among OEF and OIF military personnel and veterans. Pain severity and early symptom management influence the development of PTSD following combat injury. Depression appears to be both a contributing risk factor to postinjury PTSD, as well as a comorbidity. Pain remains a major concern for polytrauma survivors long after the initial injury. This paper contributes an analysis of empirical research that specifically examines the relationship among PTSD, depression, and pain outcomes for military personnel not only exposed to combat but also those injured serving our nation.

Figure 2-1: PRISMA Flow Diagram

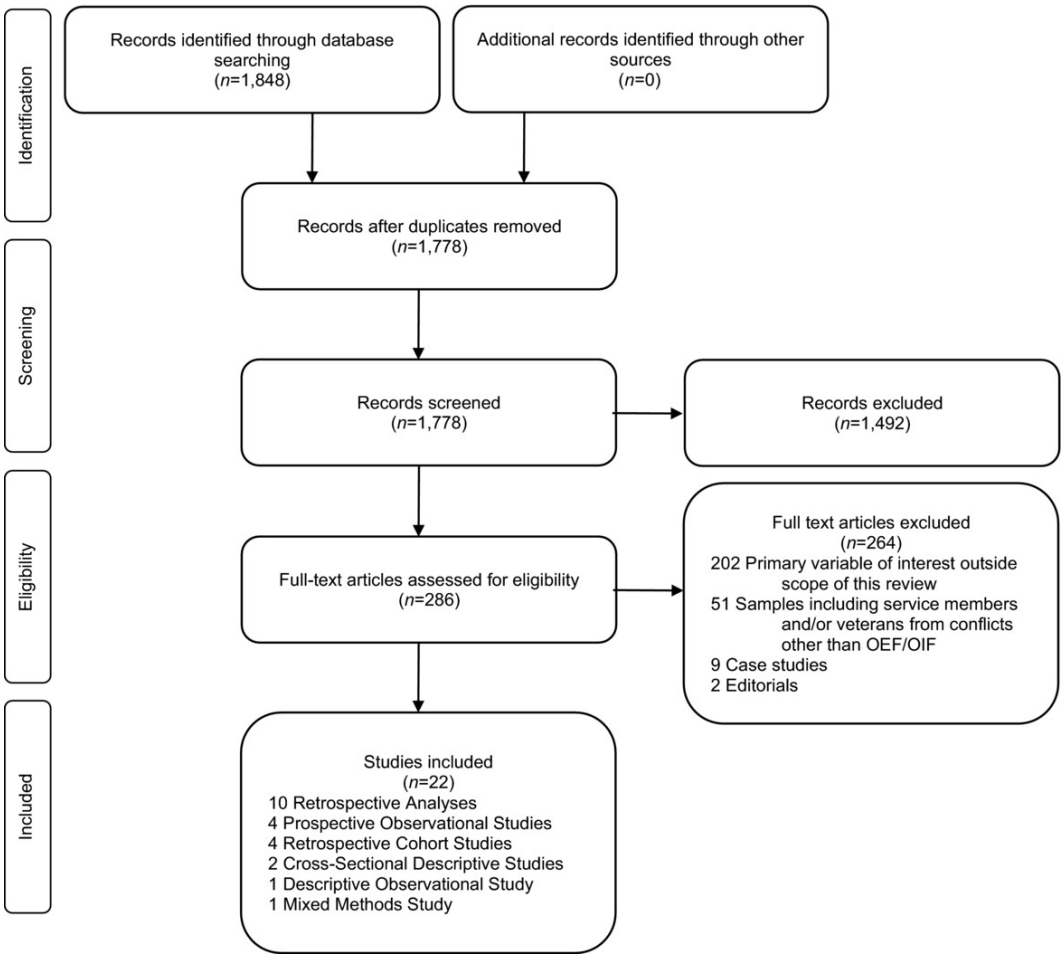

Table 2-1: Summary of Studies

Citation	Objective	Sample (setting)	Study design	Relevant findings	Relationships of key outcomes of interest	Quality of evidence [a]
Baker et al. (2009)	Examine relationship between demographic factors, military service, combat-related injury, and mental health symptoms	*N* = 339 OEF/OIF veterans (VHA)	Cross-sectional	Those who endorsed being injured during combat were more likely to screen positive for PTSD compared to those with no injuries About 37% of the sample screened positive for PTSD and about 43% reported having depressed mood within the previous month	The prevalence of disease burden and severity for both depressive mood and PTSD is higher in those with combat injuries, potentially comorbid in nature	Level 6
Buckenmaier et al. (2009)	Evaluate pain severity and emotional status of injured soldiers	*N* = 110 OEF/OIF soldiers (Landstuhl Regional Medical Center, Germany)	Mixed methods	Average and worst pain scores were negatively correlated to pain relief during transport Average pain relief in 24–48 hr after injury was less than 50% but those with a continuous peripheral nerve block reported better pain relief than those without one	Higher pain intensity scores correlate with higher anxiety, distress, and worry during transport and may be of consideration for how pain management can influence early symptoms of mental health conditions	Level 6
Buckenmaier et al. (2012)	Quantify patient-reported pain outcomes following acute pain service interventions	*N* = 71 OEF/OIF soldiers (Camp Bastion, Afghanistan)	Descriptive observational	Patients receiving peripheral nerve block reported better overall pain control compared to those receiving epidural or systematic analgesia The analgesic interventions implemented by acute pain service reduced patient-reported pain severity over the first 24 hr following combat injury	Overall mean percent reduction in pain intensity from time after initial injury to postacute pain service interventions prior to air evacuation was 60%, thereby indicating adequate acute pain assessment and management are feasible after injury	Level 6
Clark et al. (2007)	Describe innovative approaches for improving pain care provided to OEF/OIF military personnel	*N* = 50 OEF/OIF soldiers and veterans (Polytrauma Rehabilitation Center)	Cross-sectional	Regional anesthesia and continuous peripheral nerve block are most often used to manage pain after combat injury Common mental health concerns for polytrauma	The comorbid presentations of pain, PTSD, and depression are seen in polytrauma care settings in high proportions	Level 6

Table 2-1: Summary of Studies						
Citation	Objective	Sample (setting)	Study design	Relevant findings	Relationships of key outcomes of interest	Quality of evidence [a]
				service members are PTSD, adjustment disorder, and depression in this sample		
Clark et al. (2009)	Compare physical and emotional treatment outcomes of service members who sustained polytrauma injuries secondary to blast exposure compared to soldiers injured by other mechanisms	*N* = 128 OEF/OIF soldiers and veterans (Polytrauma Rehabilitation Center)	Retrospective analysis	PTSD was significantly more common among combat/blast injured cohort Functional independence measure scores were correlated to pain intensity scores for combat/blast injuries Those with combat/blast injuries had higher rates of PTSD, and any psychiatric diagnosis Combat-/blast-injured personnel experience significantly less improvement in pain severity	Injury mechanism, specifically blast, is associated with a broader spectrum of injuries, reduced improvements in pain intensity after treatment, and higher rates of psychiatric disorders	Level 4
Copeland et al. (2011)	Assess care transitions from DoD to VHA care and subsequent psychiatric care of combat-injured OEF/OIF veterans	*N* = 216 OEF/OIF veterans (VHA)	Retrospective cohort	In the sample, 38% sought care for PTSD symptoms and 27% for depression in the VHA, whereas in Department of Defense care, only 21% received a mental health diagnosis of any kind In the VHA setting, 65% of sample received pain medication	The coexistence of PTSD, pain, and depression in combat-injured veterans seeking VHA care suggests a delay in development or recognition of these trauma symptoms	Level 4
Fowler et al. (2011)	Examine the relationship of pain, injury, severity, and physiologic response in combat-injured soldiers	*N* = 2,646 OEF/OIF military personnel (JTTR)	Retrospective analysis	Pain scores were not related to physiologic parameters ISS was proportional to the pain experienced of wounded soldiers	Increasing ISS maybe proportional to pain scale responses in wounded soldiers but not for physiological responses to acute injury related stress	Level 6

Table 2-1: Summary of Studies

Citation	Objective	Sample (setting)	Study design	Relevant findings	Relationships of key outcomes of interest	Quality of evidence [a]
Grieger et al. (2006)	Examine rates, predictors, and course of PTSD and depression among seriously injured soldiers following hospitalization	*N* = 243 OEF/OIF soldiers (Walter Reed Army Medical Center, Maryland)	Prospective observational	High severity of physical problems at 1-month postinjury was significantly associated with a diagnosis of PTSD and depression over time Majority of participants with PTSD or depression at end of follow-up period (7 months) did not qualify for an initial diagnosis at 1 month after injury	Early severity of physical combat injuries, including pain severity, is strongly associated with the latent development of PTSD or depression	Level 4
Holbrook et al. (2010)	Study effect of morphine use during early resuscitation on developing PTSD in injured military personnel	*N* = 653 OIF soldiers (CTR EMED)	Retrospective cohort	The use of morphine 24 hr after injury was significantly associated with reduced risk of PTSD compared to those who did not receive morphine	Aggressive pain management in the immediate postacute injury period, specifically the use of morphine, is strongly associated with lower risk of PTSD	Level 4
MacGregor et al. (2009)	Characterize the relationship between injury-related factors and PTSD among battle-injured military personnel	*N* = 831 OIF military personnel (CTR EMED)	Retrospective analysis	As ISS increases, the odds of being diagnosed with a mental health illnesses increases Serious and severe ISS scores increased the odds of being diagnosed with PTSD	Injury severity may be a significant predictor of PTSD and other mental health diagnoses, including depression up to 6 months after initial injury	Level 4
MacGregor et al. (2009)	Describe prevalence of PTSD and self-reported mental health symptoms among OIF combatants	*N* = 1,968 OIF military personnel (CTR EMED)	Retrospective analysis	Greater risk for PTSD and other mental health diagnoses, including depression, among battle-injured than nonbattle-injured Injury severity indicated greater risk for developing PTSD or other mental health diagnoses	Compared with nonbattle injuries, those with battle injuries had a greater risk of PTSD and other mental health diagnosis, such as depression, and there was a positive association with injury severity possibly resulting from the mechanisms of battlefield-related injuries	Level 4
MacGregor et al. (2013)	Examine the association between deployment-related injury and PTSD among	*N* = 3,403 OIF military personnel	Retrospective analysis	Predictors of PTSD among those with battle injuries included moderate to serious-	The presence of mental health conditions, such as depression, may act as predisposing risk	Level 4

Table 2-1: Summary of Studies						
Citation	Objective	Sample (setting)	Study design	Relevant findings	Relationships of key outcomes of interest	Quality of evidence [a]
	battle-injured and nonbattle-injured personnel	(CTR EMED)		severe ISS, prior battle injury, and mental health diagnosis within 1 year predeployment Battle injury is a significant predictor of PTSD compared to those not injured in battle	factors for PTSD after experiencing serious-severe combat injuries	
McGhee et al. (2008)	Investigate the prevalence of PTSD in OEF/OIF service members treated for burns and administered perioperative ketamine	*N* = 147 Soldiers sustaining burns (JTTR)	Retrospective cohort	The prevalence of PTSD was lower among those receiving ketamine compared to those who did not receive ketamine	Pharmacological pain management interventions, specifically the use of ketamine after combat-related burn injuries, may act as a protective factor in developing PTSD	Level 4
McGhee et al. (2014)	Evaluate relationship between early acute pain scores and PTSD in burned soldiers	*N* = 289 Soldiers sustaining burns (JTTR)	Retrospective analysis	Despite increased ISS in combat injuries, individuals exposed to ketamine experienced no greater risk of developing PTSD as less severely injured soldiers without ketamine	Decreased PTSD development may be related to effective pain control, specifically the use of ketamine after burn injuries	Level 6
McLay et al. (2012)	Determine whether different injury mechanisms predict the risk and severity of PTSD symptoms	*N* = 1,402 OEF/OIF military service members (Naval Medical Center, San Diego)	Retrospective analysis	Service members with blunt and combined (e.g., blunt and blast) mechanisms of injury had higher symptom severity of PTSD than those with no injury or only penetrating injures	Mechanism of combat injuries (blunt trauma and blast exposure) is associated with high rates of PTSD.	Level 6
Melcer et al. (2014)	Examine short-term and long-term psychological outcomes among combat amputees	*N* = 145 OEF/OIF veterans (CTR EMED)	Retrospective analysis	Significantly reduced odds of PTSD among amputees receiving intravenous morphine compared to fentanyl over 4 years postinjury PTSD prevalence increased after first-year postinjury while rates of other	The adequate management of acute pain with morphine has shown a potentially protective effect, compared to fentanyl, on subsequent development of PTSD after combat-injured limb amputation	Level 4

Table 2-1: Summary of Studies						
Citation	Objective	Sample (setting)	Study design	Relevant findings	Relationships of key outcomes of interest	Quality of evidence [a]
				psychological illnesses decreased		
Mora et al. (2009)	Examine the association between primary blast injuries and PTSD in burned combat casualties	*N* = 333 OEF/OIF Soldiers (JTTR)	Retrospective analysis	IED wounded participants with burns and blast related injuries had increased odds of having a PTSD diagnosis compared to those with just blast injuries	Risk of developing PTSD is a function of injury type, severity, and mechanism of injury (e.g., blast)	Level 6
Phillips et al. (2010)	Explore the relationship between specific combat exposures and other life experiences with postdeployment PTSD	*N* = 706 Marines (Marine Corps Recruit Depot in San Diego, California)	Prospective observational	Marines with gunshot wounds or serious wounds were more likely to screen positive for PTSD compared to those who had neither	Rates of mental health morbidity among marines is due in part to the increased risk of PTSD associated with severe combat injury as well as individuals' traumatic psychological exposures, such as violence, prior to deployment	Level 4
Pugh et al. (2014)	Identify comorbidity clusters among veterans seeking care for deployment-specific diagnoses, including combat injuries	*N* = 191,797 OEF/OIF veterans in (VHA)	Retrospective cohort	Six clusters were identified: (a) PCT, depression, chronic disease; (b) PCT; (c) mental health and substance abuse; (d) sleep, amputation, chronic disease; (e) pain and moderate PTSD; (f) relatively healthy Depression was a significant comorbidity and characterized by PTSD when present in cluster A and C and individuals were most likely to have adverse outcomes and healthcare utilization	The comorbid nature of depression, PTSD, and pain compounds in veterans seeking care in the VHA as evident in increased complexity of care needs and care utilization	Level 4
Sandweiss et al. (2011)	Prospectively assess the relationship of predeployment psychiatric status, injury severity, and postdeployment PTSD	*N* = 22,630 Service member participants in the Millennium Cohort Study	Prospective observational	After adjusting for baseline PTSD and all other exposure variables, the odds of postdeployment PTSD symptoms were greater in those with one or more	Diagnosed mental health conditions, including depression, potentially act as predisposing risk factors for PTSD following combat injury	Level 4

Table 2-1: Summary of Studies						
Citation	Objective	Sample (setting)	Study design	Relevant findings	Relationships of key outcomes of interest	Quality of evidence [a]
		(Naval Health Research Center in San Diego, California)		defined baseline psychiatric disorders compared to those with no psychiatric disorders After adjusting for baseline PTSD symptoms, the odds of postdeployment PTSD symptoms were 16% greater for every 3-unit increase in ISS		
Sayer et al. (2009)	Describe the medical rehabilitation needs of OEF/OIF inpatients with combat injuries	*N* = 188 Military personnel and veterans (Polytrauma Rehabilitation Center)	Retrospective analysis	Pain and psychiatric symptoms were significant complaint during inpatient stay and all patients received pain management interventions Pain was present in 100% of the sample and at 50% experienced mental health symptoms	Pain is pervasive in veterans following polytrauma and requires optimal management so as to prevent interference in physical and psychological rehabilitation efforts	Level 6
Stratton et al. (2014)	Investigate the longitudinal course of pain and PTSD symptoms following blast exposure	*N* = 209 OEF/OIF Military personnel (VHA)	Prospective observational	PTSD scores and symptoms exert a strong influence on pain scores PTSD scores at baseline predict patient-reported pain scores at 6 and 12 months, whereas baseline pain scores only predict PTSD scores at 6 months	Pain and PTSD are significantly associated with one another across the care continuum when present indicating optimal management early on after diagnosis can influence symptom severity longitudinally	Level 4

Note. PTSD, posttraumatic stress disorder; IED, improvised explosive device; ISS, Injury Severity Score; PCL-M, PTSD checklist military version; OEF/OIF, Operation Enduring Freedom/Operation Iraqi Freedom; VHA, Veterans Health Administration; CTR EMED, Combat Trauma Registry Expeditionary Medical Encounter Database; JTTR, Joint Theater Trauma Registry.

[a] Level of evidence determined using rating system for the hierarchy of evidence (Melnyk & Fineout-Overholt, 2011). The hierarchy is a seven-tier scale, with the best evidence receiving the strongest rating. The strongest evidence to base clinical practice on is rated Level 1 and includes both systematic reviews and meta-analyses of randomized controlled trials or evidenced-based clinical practice guidelines based on systematic reviews of randomized controlled trials. Level 2 comprises evidence from well-designed randomized control trials, Level 3 evidence comes from controlled trials with no randomization. Level 4 contains cohort and case-control research studies. Level 5 evidence is produced from systematic reviews of descriptive and qualitative studies. Level 6 includes both single descriptive studies and qualitative work, and the weakest evidence, Level 7, is expert opinions.

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CHAPTER 3

Longitudinal Trajectories of Pain and Post-Traumatic Stress Symptoms After Exposure to Regional Anesthesia Following Combat Injury

Abstract

Unrelieved acute pain after combat injury can contribute to the development of chronic pain and post-traumatic stress disorder (PTSD). There are few studies evaluating longitudinal presentations of pain and PTSD symptoms after combat-injured patients receive acute pain management. This prospective observational cohort study evaluated the association of early pain management and PTSD symptom trajectories on pain experiences in 288 Operation Enduring Freedom and Operation Iraqi Freedom (OEF/OIF) combat-injured military personnel who received regional anesthesia (RA) or standard pain management approaches for pain management. Pain and PTSD symptoms are moderately to strongly ($r_s > .31$) positively correlated up to 21 months after injury ($P < .05$). Linear mixed effects models indicate that both initial pain intensity ($P < .001$) and initial PTSD symptom severity are strongly associated with pain intensity and interference ($P < .001$). Moreover, worsening PTSD symptom trajectories are significantly associated with higher average pain and pain right now, after controlling for injury severity, RA receipt, and time from injury to observation ($P < .02$). There are short- and long-term reductions in pain intensity with early RA administration following combat injury ($P < .01$). Evidence indicates that RA is an effective intervention and that both pain and PTSD symptoms should be evaluated and addressed on an ongoing basis in combat-injured persons.

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Perspective: RA is an effective pain intervention for trauma care and is associated with long-term reductions in pain intensity. Findings underscore the need for implementing early acute pain management interventions and for continued evaluation of pain-related outcomes and comprehensive mental health treatment approaches beyond one year after injury.

Keywords: pain interference, pain intensity, post-traumatic stress disorder (PTSD), regional anesthesia, combat injury, Operation Enduring Freedom (OEF), Operation Iraqi Freedom (OIF)

Introduction

Significant advancements in combat casualty care have increased survival rates in American military personnel sustaining complex combat injuries during Operation Enduring Freedom and Operation Iraqi Freedom (OEF/OIF).[1,2] The severity of many of these combat related-injuries warrant early and sustained pain management. However, acute pain services delivered by pain management specialists capable of providing early multimodal analgesics in the immediate aftermath of injury and throughout the military evacuation chain are still needed as part of the combat casualty care.[3,4] Evidence suggests that hyperstimulation of central neuronal pathways and unrelieved acute pain induces neural plasticity in the central nervous system and leads to maladaptive neuropathological remodeling after injury.[5,6] This rewiring may result in chronic pain and elevate subsequent risk for mental health conditions, such as post-traumatic stress disorder (PTSD), for patients who have experienced unrelieved severe pain after traumatic injury.[7-9] To date, there have been few longitudinal studies of this association after combat-related injury.

Chronic pain and PTSD are believed to share a vulnerability pathway that, when co-existing, amplify exacerbations of symptoms, increase pain intensity, and pain interference.[10-13] Pain intensity is a valuable measure of how severe pain is, and pain interference is a measure of how pain impacts physical, social, and emotional functioning.[14] Severe persistent PTSD symptoms, lasting for over one month after witnessing or experiencing a traumatic event (e.g. combat-related injury) are diagnosed as PTSD.[15] Estimates show 30%-60% of combat-injured veterans are diagnosed with

PTSD, compared to an estimated 11%-20% in the general OIF/OEF veteran population.[16,17] Additionally, 50%-80% of OEF/OIF veterans diagnosed with PTSD also report chronic pain.[17] PTSD is believed to be a risk factor for transitioning from acute to chronic pain.[18] PTSD symptom severity may be a source of variability in how veterans affected by chronic pain numerically rate their pain experience.[19] Veterans with significant PTSD symptomatology and chronic pain often experience increased pain intensity, pain interference, and pain-related disability.[20,21] Increased PTSD symptom severity is believed to significantly amplify pain perception after injury, both in civilian[22] and OEF/OIF[23] veteran populations. Others have found trauma related pain is associated with worse PTSD symptoms in veteran populations.[25]

The mutual presence of PTSD and chronic pain in OEF/OIF veterans has been investigated since the onset of these conflicts.[26-28] However, the relationship of pain and PTSD in OEF/OIF combat-injured veterans is primarily examined using cross-sectional or retrospective designs and PTSD is dichotomized as present or absent without evaluating symptom severity or symptom trajectories.[29,30] The few longitudinal investigations of pain and PTSD symptom severity in OEF/OIF military personnel and veterans are limited to one year follow up time periods, do not adjust for time since injury, depend on self-reported injury status, and do not consider early pain interventions.[31-34] Trajectories of PTSD, or longitudinal changes in total symptom severity, are generally characterized to be low-stable (resilient), worsening (chronic), or improving over time (recovery/remitting), with numerous variations in these trajectories based on time of observations and samples.[35-38] The most prevalent PTSD symptom

presentations seen in OEF/OIF military personnel and veterans is of the low-stable symptom trajectory.[35] Considering the significant impairment symptoms can have on physical and social functioning, ongoing evaluation of PTSD symptoms in this population is still warranted, even for individuals whose symptoms do not meet diagnostic criteria. Changes in PTSD symptoms, even at early stages after combat injury, have the potential to inform future care planning and monitoring for pain severity and interference.

Early multimodal pain interventions following serious injuries can mitigate the lasting effects of tissue trauma. Regional anesthesia (RA) has been shown to adequately provide acute pain management for modern combat casualties in the austere environment[40,41] and throughout transportation,[42] as well as safely deliver anesthesia and analgesia during the preoperative, intraoperative, and postoperative periods.[43] Use of RA is postulated to reduce the risks of post-surgical complications after injury.[42,50,55] Benefits of utilizing RA, over systemic analgesics and anesthetics, include the avoidance of intubation for mechanical ventilation, lower risk of hemorrhage, and more optimal postoperative analgesia.[49,55,56] Moreover, observational studies have suggested early pain management after combat-injury, with either morphine[44,45] or ketamine,[46] has a protective effect on the development of PTSD. These early pain interventions could potentially influence PTSD trajectories, which in turn effect pain intensity and interference. RA, particularly as a peripheral nerve block, can be an optimal mechanism for trauma patients with major limb injuries due to the directed delivery of analgesics without systemic effects. Over half of OEF/OIF combat-related injuries are extremity injuries[47] and about 20% of these

extremity injuries are serious and potentially fatal.[48] The purpose of this secondary analysis is to evaluate the association of RA and PTSD symptom trajectories with pain intensity and interference in a sample of combat-injured OEF/OIF military personnel and veterans.

Methods

Study Design

The Regional Anesthesia Military Battlefield Pain Outcomes Study (RAMBPOS) is a prospective observational cohort study that investigated the effects of early aggressive RA following major combat-related limb injuries sustained in the OEF/OIF conflicts by United States (U.S.) military personnel and the subsequent patient-reported pain outcomes. RAMBPOS enrollment began in October 2007 and data collection concluded in September 2014. The research team at Corporal Michael J. Crescenz Veterans Affairs (VA) Medical Center (Philadelphia, PA) collected participants' patient-reported outcomes via telephone. Attempts were made to collect patient-reported outcomes monthly for individuals joining the study within the first 6 months after injury and every 3 months thereafter, for up to 24 months after combat injury. Individuals could join the RAMBPOS study at any time after injury. Interviews with participants collected data on pain intensity and interference, and mental health symptom severities, including PTSD. Medical record review from The Department of Defense's (DOD) Joint Theater Trauma Registry, now known as the DOD Trauma Registry, provided clinical and military career information, including date of injury, pain management and treatment status, and Injury Severity Score (ISS). IRB approval for this secondary analysis was provided by the

Department of Veterans Affairs (VA) Medical Center Research & Development Committee and the University of Pennsylvania.

Participants

Participants were recruited from the former Walter Reed Army Medical Center (Washington, DC), the current Walter Reed National Military Medical Center (Bethesda, MD), and the U.S. Army Institute of Surgical Research at Brooke Army Medical Center (San Antonio, TX). Participants with a combat-related major injury in one or more extremities requiring hospitalization were eligible for enrollment in RAMBPOS. Exclusion criteria included: moderate and severe traumatic brain injury (TBI), cognitive deficits, inability to concentrate, poor judgment and impulse control, substantial hearing loss, and bilateral upper extremity amputation with no alternate means to complete the survey forms. Of the Six-hundred and eighty-seven (N = 687) combat-injured military service members screened while inpatients or in rehabilitation, 301 did not meet eligibility criteria for study enrollment. Three-hundred and eighty-six (N = 386) participants consented, enrolled and provided data in RAMBPOS. Analysis was only possible on participants with two or more patient-reported pain outcomes and PTSD assessments, and 98 participants did not meet these criteria. The final sample for this secondary analysis included 288 combat-injured military personnel with two or more pain and mental health assessments within 24 months after injury. There was a mean of 7.47 observations per participant.

Regional Anesthesia

Under ultrasound imaging an epidural or a peripheral nerve block, either intermittent or continuous, is placed near a cluster of nerves through which RA is delivered to an area of the body that requires localized pain management, such as a severely injured extremity.[53,54] RA, specifically peripheral nerve blocks, have been used to manage pain in the austere environment, during transportation, preoperatively, and during acute care following injuries in both Iraq and Afghanistan.[3,41,42] Whether individuals received RA, or not, was based on their proximity to a forward operating base, within a combat support hospital, with a trained military anesthesia provider, and acute pain service deployed at time of injury, as well as the availability of these services upon arrival in a U.S. military hospital. RAMBPOS individuals who received RA within 14 days after injury were compared to individuals who did not receive RA within 2 months after injury. RA receipt was confirmed in the medical and surgical records upon enrollment. Participants not receiving RA still received standard pain management including systemic multimodal pain management throughout transportation and acute care at U.S. military medical facilities. These consented and enrolled participants constitute the No RA cohort. RA was the independent variable for this study.

Measures

Brief Pain Inventory

The Brief Pain Inventory (BPI) is a 9-item pain assessment tool measuring pain intensity and pain interference.[57] One of the strengths of the BPI is its ability to measure the multiple dimensions of pain, including asking respondents to reflect on the extremes of

their pain experience, worst pain and least pain, to better contextualize the pain they are reporting at time of assessment. Respondents rate their worst pain in the past 24 hours, least pain in the last 24 hours, average pain, and pain right now (at time of assessment), intensity on a scale of 0-10, with 0 being "no pain," and 10 being "pain as bad as you could imagine." The interference section of the measure includes ratings for the degree to which pain interferes with general activity, mood, walking, work, relationships, sleep, and enjoyment of life from 0, "pain does not interfere", to 10, "interferes completely", collectively known as pain interference.[58,59] The BPI has been validated to accurately assess for noncancer pain,[60] chronic nonmalignant pain,[61] and individuals experiencing pain from orthopedic injuries.[62] BPI pain intensity measures for worst, least, average, and pain right now were each examined as primary outcomes. Pain interference was also a primary outcome and scored as the mean of the seven interference items (i.e. general activity, mood, walking, work, relationships, sleep, enjoyment of life).

Post-traumatic Stress Disorder Checklist

The Post-Traumatic Stress Disorder Checklist Military Version (PCL-M) is a 17-item validated PTSD assessment instrument. Respondents rate the extent to which they have experienced each of the 17 diagnostic symptoms for PTSD outlined in the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV), as related to stressful military experiences.[63-65] Total symptom severity scores are computed by adding the 17 items, with each item scored based on the degree to which the symptoms bothered a participant over the past month from "not at all" (1) to "extremely" (5). Total PCL-M scores range from 17 to 85. The PCL-M can provide a presumptive diagnosis for PTSD.[66] The VA

National Center for PTSD recommends a minimum threshold of 30 for total symptom severity score on the PCL-M be considered meeting PTSD diagnostic criteria.[66] RAMBPOS participants completed the PCL-M as part of the battery of mental health assessments provided by the Philadelphia VA Medical Center's Behavioral Health Lab, which is part of the VA's measurement based mental health care initiative. PTSD was examined as a covariate in this analysis.

Other Characteristics

The screening and baseline interviews assessed sociodemographic characteristics (e.g. age, gender, race, ethnicity, education, marital status). Other covariates included the length of hospitalization (in days), number of deployments, and Injury Severity Score (ISS).

Injury Severity Score

The ISS is a scale used to evaluate anatomic injury severity following traumatic injury that ranges from 0 to 75, with 75 indicating the greatest severity and incompatible with life.[67,68] The ISS is based on an Abbreviated Injury Scale (AIS) score allocated to the six body regions (i.e. Head, Face, Chest, Abdomen, Extremities, and External). The highest AIS score in each body region is used. The three most severely injured body regions scores are squared and summed to produce the ISS. The ISS correlates linearly with mortality, morbidity, hospital stay and other measures of severity. In this analysis ISS was examined both linearly and categorically as Minor (≤9), Moderate (10-15), Moderate/Severe (16-24), and Severe/Critical (≥25). The ISS is one of the most consistently used numeric tools for quantifying trauma severity available in the DOD's

medical health records since the onset of either armed conflict.[69] ISS was a covariate in this analysis.

Statistical Analysis

Descriptive Statistics

Univariate descriptive statistics for both the RA and No RA cohort were calculated. Bivariate statistical tests were conducted to assess if there were any statistically significant differences between sociodemographic and injury variables, with and without RA administration. Between group differences were compared with independent sample t-tests or chi-square tests at baseline. Average PCL-M scores were compared between RA cohorts.

PTSD Symptom Severity and Pain Intensity and Interference Correlations

The positive relationship between PTSD and pain intensity and interference was visually inspected using bivariate scatter plots **(Appendix Figures A3-1 to A3-5)**. Spearman's correlation estimates (r_s) were calculated at each time point (i.e. month since injury to observation), due to the non-normal distributions of PCL-M scores (Shapiro-Wilk = .834, $P < .001$). This was done to assess the monotonic relationship between pain intensity and interference, each separately, with PTSD symptom severity, using the PCL-M. Correlation coefficients were categorized based on well-established guidelines.[70]

PTSD Symptom Trajectories

For this analysis, PTSD symptom severity was examined based on PCL-M total symptom severity scores. Models included participants' first PCL-M scores in the study, referred to as an initial PTSD presentation. The primary interest was the change over time in pain

and PTSD. However, baseline values included in the modeling controlled for intraindividual variability. Next, PTSD symptom trajectories were calculated as the overall difference in an individual's first PCL-M score and an individual's last observed PCL-M score, over the time difference:

$$m_{PCL\ Slope} = \frac{y_{Last\ PCL\ Score} - y_{First\ PCL\ Score}}{x_{Last\ Month\ PCL\ was\ Observed} - x_{First\ Month\ PCL\ was\ Observed}}$$

PTSD symptom trajectories were characterized (**Figure 3-1**) from a continuous variable into an indicator term: (1) individuals with a worsening trajectory (e.g. PTSD symptoms increase over time), (2) individuals with stable trajectories (e.g. PTSD symptoms do not get better or worse), and (3) individuals with an improving trajectory (e.g. PTSD symptoms decrease over time). This was done to maximize the number of participants in the improving and worsening trajectories to better assess the effects of either trajectory. Sensitivity analyses were conducted with a wider caliber for the stable trajectory (See Appendix **Table A3-2**). Distribution of PTSD symptom trajectory categories were examined across each RA cohort. Of note, unadjusted least squares linear regression slopes were fitted and found to be of poorer fit than using the two-point derived slopes to estimate pain outcomes (Likelihood-ratio test, $\chi^2 = 35.96$, $P < 0.001$).

Time

Time was defined as the number of months since injury that a pain outcome measure was observed (i.e. months 0 to 24). When used as a continuous random-effect in the model, time accounts for both within and between subject variability in point estimates. All individuals in this analysis had at least two-time points separated by at least one or more

months. Therefore, a random intercept unique to each individual was used in the model parameter estimates. An indicator variable for time since injury and time to first observation in the study, known as the study entry cohort, was included in the model to account for potential selection bias. The study entry cohorts were categorized as less than 6 months, between 6-12 months, or over 12 months since injury. The majority of participants, 76.74%, entered the study within 6 months of injury, 15.97% entered between 6 months to a year after injury, and 7.69% of participants entered over a year after injury.

Mixed Effect Models

Linear mixed effects models examined whether longitudinal progression of the outcomes, pain intensity and pain interference, are associated with an individual receiving RA and PTSD symptom trajectories. Linear mixed effects models are extensions of simple linear models, such as linear regression, and incorporate both fixed and random effects.[71,72] This approach accounts for collinearity between individuals' repeated outcome measures. First, bivariate models were fit to assess the association of each fixed effect (e.g. RA receipt status, ISS, length of hospitalization) to pain outcomes. A forward stepwise variable selection process was utilized. Goodness of fit for each model was assessed using Akaike information criterion (AIC).[73] Each model includes a random intercept and slope to account for individual differences in the time between injury to observation (i.e. the number of months after injury that the outcome measure was recorded per person). Both a model with random intercept only, and a model with random slope only were assessed for goodness of fit and compared to the combined random intercept and slope

model. The combined intercept and slope model was determined to be best fitting based on AIC to account for time since injury and time of observation per person.

Mixed effects models were constructed to evaluate the association of initial PTSD clinical presentations on estimating pain intensity and interference, separately. Both the initial PTSD clinical presentations and the symptom trajectories are treated as fixed-effects in the models. Sensitivity analyses included generating models after controlling for baseline pain intensity and interference. Interaction terms between treatment (RA) and time (month since injury) were not significant and did not increase model fits compared to those models without interaction terms, based on AIC. Initial BPI measures, or an individual's baseline, were used in sensitivity analyses. Given the difference in the spacing of measurements and AIC values, an identity covariance matrix was used to account for the model residuals. Model parameters were estimated using maximum likelihood with degrees of freedom derived using the Satterthwaite method, after comparing against full restricted maximum likelihood estimation (REML) for parameters.[74,75] A *P*-value less than .05 was considered significant. All analyses were conducted with Stata® 15.0 (Stata Corp SP, College Road, TX, USA).

Results

Descriptive Statistics and Baseline Associations

The sample, at baseline, was predominately young (28.10 years old, +/- 7.00), White (76.39%), and almost exclusively male (98.96%) (**Table 3-1**). In this sample, 149 participants received RA and 139 participants did not receive RA within two weeks of injury. The cohorts were statistically equivalent on most sociodemographic and injury

characteristics, except for marital status (P = .032) where the RA cohort had a higher percentage who were married (55.70% compared to 41.01%), and an average length of hospitalization (P < .001) about 14 days longer (44.10 days compared to 29.90 days). There was no significant difference in the proportion of individuals meeting diagnostic levels of PTSD at time of entry into the study. Mean PCL-M total symptom severity score at baseline was not statistically different between the RA cohorts and the proportion of individuals with slope changes worsening, improving, or stable was not significantly different between cohorts. The average PCL-M score among individuals with worsening PTSD symptom trajectories (30.60 +/- 13.44) was highest compared to those with an improving PTSD (26.80 +/- 11.40) symptom trajectory and those with a stable trajectory (21.00 +/- 8.61). The time to entry in study and symptom trajectory interaction term was not significant, indicating there was no effect of entry on PTSD symptom severity.

Longitudinal Associations with Pain Intensity, Interference, and PTSD

Worst pain and PCL-M score correlation coefficients indicated a moderate positive monotonic relationship ($r_s \geq .51$) at several time points within, and at the first 12 months after injury (i.e. months 6, 10, 12) and beyond up to 14 months after injury. The correlations at these time points were significant (P < .02). A moderate positive correlation coefficient between least pain and PCL-M was seen at 6 months (P = .007) and again at 13 months (P = .001). There was a high positive correlation ($r_s \geq .71$) between, average pain and PCL-M at 6, 13, 16 months that is statistically significant (P < .010. Pain right now and PCL-M were statistically significantly associated, with high positive monotonic relationship seen at 6, 13, and 16 months after injury (P < .01). This

strong association, high positive correlation, was seen between pain interference and PCL-M scores exclusively after one year of injury, at months 16, 17, and 18 months ($P < .05$). However, moderate positive correlation coefficients were seen between pain interference and PCL-M that were statistically significant across the first two years after injury and up to twenty-one months. A statistically significant low to moderate positive correlation is seen up to twenty-one months after injury for all pain intensity and interference measures, except least pain. These findings are illustrated in **Table 3-2**. A low negative correlation, between all pain outcomes and PCL-M scores, was observed at under one month after injury, however this association was not statistically significant.

Initial Presentations of Pain and PTSD Mixed Effects Models

A set of models was constructed to evaluate how an individual's initial PTSD presentation was associated with pain intensity and interference, over time in the study (**Table 3-3**). The treatment effect of RA on mean worst pain, least pain, average pain, and pain right now was statistically significant, indicating better pain management compared to those without RA ($\beta = -.393$, $P = .001$; $\beta = -.263$, $P < .001$; $\beta = -.373$, $P < .001$; $\beta = -.0274$, $P = .006$, respectively). The treatment effect was not significant for pain interference. The time by treatment interaction was not significant and not included in the final analysis. Estimates for worst pain, average pain, pain right now, and pain interference decrease, with statistical significance, with each month after injury ($\beta = -.031$, $P = .001$; $\beta = -.028$, $P < .001$; $\beta = -.019$, $P = .013$; $\beta = -.040$, $P < .001$, respectively). Length of hospitalization remained statistically significant in estimating worst pain ($\beta = .006$, $P = .007$), average pain ($\beta = .003$, $P = .037$), and pain interference ($\beta = .006$, $P =$

.001), with increased length of stays associated with increased patient-reported pain outcome estimates, adjusting for all other variables. However, given the small parameter estimates, this effect is not clinically meaningful. ISS was not statistically significant in the estimates of the association with any pain intensity and interference outcome. However, ISS and length of hospitalization were moderately positively correlated (Appendix **Figure A3-1**). Married participants experienced statistically significantly higher pain scores for worst pain, pain right now, and pain interference (β = .364, *P* = .001; β = .211, *P* = .032; β = .499, *P* < .001, respectively), when compared to the single participants. Being a divorced or separated participant was associated with the highest pain interference scores, compared to single participants (β = .650, *P* = .001). Time to entry in the study was significant in estimating the association with pain intensity and interference. Individuals entering the study after one year of injury were estimated to have statistically significantly higher worst pain, least pain, average pain, and pain right now (β = 1.010*, P* = .003; β = .476, *P* = .020; β = .674, *P* = .008; β = .629, *P* = .048, respectively).

Initial PCL-M scores were statistically significant (*P* < .001) in the model estimating the association with all pain outcomes. More symptomatic individuals, or those with elevated PCL-M total symptom severity scores, were estimated to have higher BPI pain intensity (i.e. worst, least, average, and pain right now) and interference scores. PCL-M scores remained statistically significant even after adjusting for initial pain presentations in the model. For example, including mean initial average pain scores in the model was found to have a statistically significant effect on estimating future average pain, on the

BPI (β = .545, $P < .001$). This indicates that elevated pain intensity and interference upon entry into the study, across all BPI measures, are associated with higher estimated pain outcomes in the future ($P < .001$).

PTSD Symptom Trajectory Mixed Effects Models

Individuals receiving RA experienced less intense worst pain, least pain, average pain and pain right now scores than the comparative non-RA cohort at any time point (β = -.353, $P = .002$; β = -.253, $P < .001$; β = -.343, $P < .001$; β = -.274, $P = .006$, respectively) (**Table 3-4**). **Figures 3-2** to **3-6** illustrate this association between RA receipt and pain outcomes. RA was not statistically significantly associated with pain interference. The time by treatment interaction term was not significant and was not included in the analysis. Time since injury, measured in months, remained statistically significant in models for worst pain, average pain, pain right now, and pain interference, indicating that over the course of the study, patient-reported pain intensity and inference decreased (β = -.030, $P < .001$; β = -.027, $P < .001$; β = -.017, $P = .031$; β = -.037, $P < .001$, respectively). Time since injury was not statistically significant in estimating least pain. Alternatively, longer length of hospitalization after initial injury, measured in days, led to small incremental, and statistically significant, increases in patient-reported pain outcome scores (worst pain, β = .006, $P = .010$; least pain, β = .002, $P = .047$; average pain, β = .003, $P = .037$; pain interference, β = .005, $P = .002$). ISS was not statistically significant in any model estimating pain outcomes, indicating that there is no statistical difference in pain intensity and interference estimates by injury severity.

Other covariates were found to be associated with pain intensity and interference. This includes a participant's marital status. Being married, or having a partner, was associated with participants reporting higher worst pain (β = .331; *P* = .004), pain right now (β = .201; *P* = .046), and pain interference (β = .456; *P* < .001), compared to single participants. Divorce or separated participants experienced the highest pain interference compared to single participants (β = .766; *P* < .001) Late entry to the study (i.e. more than 1 year after injury) was again associated with experiencing higher worst pain intensity, but not pain interference (worst pain, β = 1.067; *P* = .002; least pain, β = .566; *P* = .006; average pain, β = .741; *P* = .004; pain right now, β = .740). First pain measures were associated with the largest coefficients of pain outcomes (worst pain, β = .607; *P* < .001; least pain, β = .577; *P* < .001; average pain, β = .581; *P* < .001; pain right now, β = .588; *P* < .001; pain interference, β = .578; *P* < .001).

There was a statistically significant difference in the worst pain, average pain, pain right now, and pain interference estimates based on PTSD symptom trajectories (**Table 3-4**). Worsening PTSD symptoms were associated with higher pain intensity. When compared to those with improving PTSD symptom trajectories, individuals with worsening PTSD symptom trajectories experienced higher average pain (β = .203, *P* = .018), and pain right now (β = .373, *P* < .001), controlling for all other covariates and accounting for RA status. However, individuals with stable PTSD symptom trajectories were estimated to have a statistically significant decrease in their worst pain (β = -.384, *P* = .049), and pain interference (β = -.511, *P* = .001) compared to those with improving PTSD symptom trajectories. PTSD symptom trajectories were not associated with least

pain outcomes. This differential pain response by PTSD symptom trajectory is most evident when graphing the marginal linear estimates (**Figures 3-7 to 3-11**).

Discussion

The findings from this analysis identified that initial PTSD symptom severity and PTSD symptoms trajectories were associated with statistically significant changes in pain intensity and interference. Additionally, combat-injured military personnel and veterans receiving RA had lower patient-reported pain outcomes than individuals not receiving RA. RA is an effective pain management intervention for controlling pain following combat-related injuries.[41,50,51,76,77] Findings demonstrate the potential long-term benefits of early RA in a combat-injured cohort, seen months after initial RA treatment. This is evident by a decrease in all pain intensity measures over time compared to individuals not receiving early aggressive multimodal RA. Other investigations have found RA to improve the pain experience after combat injury, however, these studies are often limited to showing the short-term advantages of RA.[3,42,78,79] Often study periods fall short of capturing the lasting benefits of early aggressive pain management with RA, as accomplished in this study. Other cross-sectional studies of combat-injured service members, and prospective studies of shorter duration, clearly support that RA is responsible for improvements in pain outcomes.[4,51,78] The prospective longitudinal investigation of RAMBPOS enables the simultaneous evaluation of the association of PTSD symptoms and pain, unlike other investigations of early acute pain management which are cross-sectional or retrospective in nature. The ability to observe differences in pain intensity and interference, and PTSD symptom trajectories in a longitudinal manner

is critically important to justify the sustained value of early RA.

There is a low to moderate positive correlation between worst pain and PTSD, least pain and PTSD, and average pain and PTSD total symptom severity up to twenty-one months after injury. Pain interference and PTSD total symptom severity are positively correlated at multiple times within one year after injury. However, the strongest association between conditions are seen beyond one year after injury. Correlation coefficients are similar to shorter year-long investigations of PTSD and pain among veterans, which also found symptoms to be significantly moderately correlated.[25,33]

In this study, the initial PCL-M score was significantly associated with pain intensity and interference. This supports other's findings that PTSD symptoms are found to be significantly associated with higher patient-reported pain after injury.[32,33] There is a well-established relationship between the mutual presentations of PTSD and pain after experiencing a combat-related injury.[80-82] However, this study differs from previous studies examining the presence of these mutual conditions with single items, and instead utilizes a validated multi-item patient-reported pain scale, the BPI.[25] In RAMBPOS, participants with stable PTSD symptom trajectories had the lowest pain intensity, followed by those with improving PTSD symptom trajectories, and finally individuals with worsening PTSD symptom trajectories experienced the highest pain intensity, specifically average pain and pain right now. Both Stratton et al. and Jenewein et al., identified that PTSD symptom severity significantly impacted pain intensity in participants up to a year after enrollment in their respective studies, but pain did not exert the same strength on predicting PTSD.[33,83] Vaughan et al. and Bartoszek et al. have

demonstrated that pain intensity influences exasperations of specific PTSD symptoms.[25,32] Conversely, considering Alschuler et al. found that PTSD symptom severity may cause variability in pain outcomes, further evaluation of the effects of PTSD on pain intensity and interference is warranted.[19,84] Additionally, other longitudinal investigations between PTSD symptoms and pain are often limited to one year and are not specific to OEF/OIF combat-injured American military personnel and veterans.[25,32,33,83] The average PCL-M scores per PTSD symptom trajectory group in this analysis (e.g. stable, worsening, improving), are slightly lower those seen in larger cohorts reported by both Bonanno et al.'s and Berntsen et al.'s studies of non-combat injured OEF/OIF personnel.[38,85]

This secondary analysis investigated the influence of selected covariates in the mixed effects model on pain, after receiving RA. Worsening PTSD symptom trajectories, marital status, month of observation, prolonged length of hospitalization, entering the study more than a year after injury, and initial pain intensity were associated with poorer pain outcomes. Consistent with previous findings in the injury literature, pain intensity and interference decrease with time.[33] Initial pain intensity and interference were significant indicators of future pain outcomes, which is comparable to other investigators' findings that initial pain intensity predicts pain up to six and twelve months later.[33,86] Anatomic injury severity was not significant in predicting longitudinal pain intensity or interference in the RAMBPOS population, which is consistent with some civilian research. [83] However, other authors have questioned the utility of the ISS in accurately capturing the severity of penetrating injuries and military combat-related trauma and the

need for physiologic indicators of injury severity.[87] The moderate positive correlation between ISS and length of hospitalization could potentially reduce the effect of ISS in the final model, despite fitting the data most appropriately. Other factors in our study included that married individuals, compared to single combat-injured military personnel and veterans, experienced poorer pain intensity. Divorced and separated participants had higher pain interference than single participants. Length of hospitalization after injury was significant in estimating pain outcomes, and while consistent with other's findings, the effect has little clinical value.[88] The small number of individuals entering the study a year after injury reported higher pain intensity and interference, compared to those enrolled closer to time of injury. While this could introduce sample bias, this small number of participants was evenly distributed between RA and No RA cohorts. There was no difference between cohorts by age, sex, race, education, or number of deployments and were not included in the final analysis. This sample consisted of mostly white males and therefore insufficiently powered to detect pain outcomes across racial status or sex. A large proportion of participants in the parent study had less than two PCL-M observations and were therefore not included in this analysis. The PCL-M was a secondary outcome in RAMBPOS that was less frequently collected compared to the BPI

Advancing current understanding of symptom trajectories will allow scientists and clinicians to better plan for the long-term health care requirements of populations with serious injuries. Patients, families, and health providers recognize the health needs of individuals with serious injuries continue long after acute care.[89] Introduced more than two decades ago, multimodal analgesia is currently recommended for treating both acute

and chronic pain.[40] The synergy created when multimodal regimens are used to target discrete components of the peripheral and central pain pathways provides effective analgesia at lower opioid dosing, reducing related risk and producing fewer adverse effects.[90] Advanced training of anesthesiologists and certified registered nurse anesthetists in RA is critical to ensuring that optimal pain management approaches are available to improved recovery of all injured persons.[91] Importantly, advanced pain providers do not exist in silos, and combat-injured veterans depend on the support of interdisciplinary care providers, including mental health providers.[80,92] Given the significant role PTSD symptom trajectories were found to have in this analysis, clinicians noticing changes in symptom trajectories of PTSD in military personnel and veterans during their prolonged rehabilitative care should consider the implications these changes have on pain outcomes. Due to the co-occurring nature of these conditions, and the potential for individuals to underreport PTSD symptom severity, integrated pain and mental health symptom assessments are key to connecting patients to treatment for underlying psychological contributions of pain. Systematic observation of symptom severities requires that individuals with combat injuries be assessed using standardized mental health and pain screenings, including population specific tools such as Pain Assessment Screening Tool and Outcomes Registry (PASTOR®) and the Defense and Veterans Pain Rating Scale (DVPRS).[93,94]

It is important to consider limitations of this research, many of which are common with longitudinal observational studies and investigations with recently injured military and veteran populations. Given the challenges of recruiting and retaining a sample of

combat-injured participants, there was a high degree of variability as to when participants entered the study and how long they remained in the study. For recruitment, every effort was made to enroll participants at the time of discharge from acute care at only two military hospitals in the US. Extended follow-up of these patients was further complicated by the dispersion of subject across the U.S. following discharge. This created considerable challenges in finding and following subjects, and thus, patient-reported outcome data was available for an average of about 7.5 time points for each patient, ranging from 2 to 12 observations, and not available on all patients at all time points (Appendix Table A3-1). It is hypothesized that the lack of participation was predominately driven by the challenges of re-integration and large movement of soldiers upon returning to the U.S. One might expect people with fewer problems to be less likely to respond so our sample may be biased towards those with more difficult problems. This would tend to push results towards the null, and considering there was a difference at all, supporting RA was effective on improving pain outcomes, is an indication that the difference is more likely to represent the true effect of the treatment. Unlike other methods used to assess the relationship between PTSD symptom severity and pain, modeling approaches in this analysis are not as sensitive to data missing at random and can adjust for disparate data points in the analysis. Mixed effects models utilize all available data, while simultaneously adjusting for correlation between an individual's repeated observations even when observations are unequally spaced.[72] This modeling approach estimates average time trends for entire treatment groups, or in this case RA vs No RA, and individual's responses over time, even when data are missing at random.

Additionally the almost exclusively male sample limits the generalizability of findings to female combat-injured military personnel.

Even with these limitations, the RAMBPOS is one of the most comprehensive repeated measures datasets of multivariable patient-reported pain and pain-related outcomes to examine the effects of early RA after injury. An individual's likelihood of receiving RA was not randomized given the ethical considerations, but rather based on the time of deployment and proximity to a trained RA provider at time of injury in the austere combat environment and throughout acute care in a U.S. military healthcare facility. Patients with similar injuries may or may not have received RA based on factors independent from the study, which should reduce potential selection biases between the RA cohorts. PTSD symptom manifestation can take several weeks to months to present clinically and therefore the linearity imposed on the PTSD trajectories may not accurately capture variability in presentations. Further, this analysis examined total PCL-M total symptom severity scores and did not consider the effects of specific PTSD symptoms on pain outcomes. RAMBPOS participants' PTSD total symptom severity was measured using the DSM-IV criteria, which has been found to identify similar prevalence rates of PTSD as the more recent DSM-5 criteria in OEF/OIF veteran populations.[95] All individuals in the sample experienced a mild TBI (mTBI), due to their proximity to improvised explosive devices and subsequent blast exposure. Moderate and severe TBI have been found to influence pain,[96] but mTBI alone has not been found to be associated with increased pain. While this study examined the effects of PTSD symptom trajectories on pain outcomes, it has been proposed this relationship is bidirectional with the negative

impact of PTSD symptoms on chronic pain, and vice versa.[8] Strengths of the current study include the ability to account for time since traumatic combat injury to observation in order to provide longitudinal estimates of outcomes, and the adjustment for initial acute pain management interventions considering the influence this may have on PTSD and pain.

Conclusion

RA is an effective acute pain management intervention when used as part of an interdisciplinary approach to comprehensive trauma care. RA is associated with long-term benefits in reducing pain intensity after combat injury. PTSD, pain intensity, and interference are correlated in the initial months after injury and up to twenty-one months after, which suggests that better pain control may help reduce PTSD. There are also differential responses in pain intensity and interference based on PTSD symptom trajectories. Individuals with worsening PTSD symptom trajectories are estimated to experience higher average pain and pain right now following combat injury compared to individuals with improving PTSD trajectories. Findings underscore the need for early aggressive pain therapy including RA after serious injury. Continued evaluation of both pain-related outcomes and PTSD symptoms, have the potential to inform the development and implementation of comprehensive rehabilitative services after injury.

Table 3-1: Sample Characteristics							
	Total N=288	**No RA n=139**		**RA n=149**		**Test Value**	**P - Value**
Age[a]							
Mean	28.10	28.30		28.00		0.39	0.698
Std. dev.	7.00	7.90		6.10			
Sex[b]							
Female	1.04%	1.44%	2	0.67%	1	0.41	0.521
Male	98.96%	98.56%	137	99.33%	148		
Race[b]							
White	76.39%	74.82%	104	77.85%	116	4.54	0.103
Black	4.51%	7.19%	10	2.01%	3		
Other	19.10%	17.99%	25	20.13%	30		
Ethnicity[b]							
Hispanic	12.85%	10.79%	15	14.77%	22	1.01	0.314
Not Hispanic	87.15%	89.21%	124	85.23%	127		
Education[b]							
HS Grad/GED	42.36%	44.60%	62	40.27%	60	5.49	0.064
Some College	39.58%	43.17%	60	36.24%	54		
College Grad	18.06%	12.23%	17	23.49%	35		
Marital Status[b]							
Single	45.49%	51.08%	71	40.27%	60	6.88	0.032
Married/Partnered	48.61%	41.01%	57	55.70%	83		
Separated/Divorced	5.90%	7.91%	11	4.03%	6		
Number of Deployments[a]							
Mean	2.00	1.90		2.02		0.38	0.809
Std. dev.	1.09	1.10		1.09			
Length of Stay in Hospital[a]							
Mean	34.55	29.90		44.10		-3.70	<.001
Std. dev.	30.30	33.10		32.30			
Injury Severity Score[a]							
Mean	17.77	17.72		17.83		-0.09	0.930
Std. dev.	10.13	10.88		9.43			
ISS Category[b]							
Minor (≤9)	21.18%	24.46%	34	18.12%	27	2.69	0.442
Moderate (10-15)	24.65%	23.02%	32	26.17%	39		
Serious (16-24)	34.03%	30.94%	43	36.91%	55		
Severe (≥25)	20.14%	21.58%	30	18.79%	28		
PTSD Diagnosis when Entering Study[b]							
No	36.37%	74.82%	104	74.50%	111	0.83	0.361
Yes	12.24%	25.18%	35	25.50%	38		
PCL-M Score[a]							
Mean	29.59	29.00		30.12		-0.37	0.711
Std. dev.	14.30	14.00		14.80			
PCL-M Symptom Trajectory[b]							

Table 3-1: Sample Characteristics							
	Total N=288	**No RA n=139**		**RA n=149**		**Test Value**	**P - Value**
Improves	49.90%	46.60%	57	0.50	62		
Stable	13.40%	11.90%	13	0.12	16	0.20	0.905
Worsens	36.70%	41.50%	69	0.38	71		
Observations Per Participant							
Mean	7.47	7.50		7.44		0.53	0.592
Std. dev.	2.57	2.44		2.71			
Time Since Injury to Entering Study[b]							
≤ 6 Months	76.74%	80.58%	112	73.15%	109		
6 Months ≤ 1 Year	15.97%	13.67%	19	18.12%	27	2.28	0.320
> 1 Year	7.29%	5.76%	8	8.72%	13		
PTSD Improving (PCL-M Score)[a]							
Mean	26.80	26.74		26.80		-0.05	0.961
Std. dev.	11.40	11.61		11.25			
PTSD Stable (PCL-M Score)[a]							
Mean	21.00	21.06		20.98		0.05	0.962
Std. dev.	8.61	9.48		7.87			
PTSD Worsening (PCL-M Score)[a]							
Mean	30.60	30.69		30.52		0.11	0.914
Std. dev.	13.44	13.27		13.62			
Worst Pain (BPI Score) [a]							
Mean	4.86	5.03		4.71		1.06	0.290
Std. dev.	2.53	2.67		2.41			
Least Pain (BPI Score)[a]							
Mean	1.13	1.10		1.14		-0.28	0.783
Std. dev.	1.44	1.40		1.48			
Average Pain (BPI Score)[a]							
Mean	2.42	2.57		2.27		1.35	0.179
Std. dev.	2.20	1.86		1.92			
Pain Right Now (BPI Score)[a]							
Mean	1.93	1.92		1.93		0.04	0.966
Std. dev.	1.80	1.97		1.80			
Pain Interference (BPI Score)[a]							
Mean	1.81	1.89		1.74		0.59	0.555
Std. dev.	1.57	2.32		1.94			

[a] t-test [b]chi-square Coeff.=coefficient; Std. dev=standard deviations; BPI=Brief Pain Inventory; ISS= Injury Severity Score PCL=PTSD Checklist

Table 3-2: Pain Intensity and PTSD Spearman's Rank Correlation Coefficients (r_s) , by Month Since Injury (*N=288*)

Little if any correlation	Low positive (negative) correlation	Moderate positive (negative) correlation	High positive (negative) correlation
.00 to .30 (.00 to -.30)	.31 to.50 (-.31 to -.50)	.51 to .70 (-.51 to -.70)	.71 to 1.00 ≤ (-.71 to -1.00)

Month	Worst Pain			Least Pain			Average			Pain Right Now			Pain Interference		
	Obs.	r_s	P Value	Obs.	r_s	P Value	Obs.	r_s	P Value	Obs.	r_s	P Value	Obs.	r_s	P Value
0	8	-0.43	0.288	10	-0.16	0.655	10	-0.13	0.719	10	-0.33	0.351	10	-0.01	0.987
1	66	0.37	0.002	77	0.33	0.003	77	0.40	<0.001	77	0.32	0.004	76	0.43	<0.001
2	57	0.12	0.383	63	0.11	0.374	63	0.19	0.127	63	0.21	0.1	59	0.43	<0.001
3	30	0.40	0.027	36	0.22	0.193	36	0.43	0.009	36	0.26	0.1	34	0.53	0.001
4	22	0.30	0.181	28	0.33	0.082	28	0.43	0.023	28	0.55	0.003	24	0.63	0.001
5	19	0.26	0.291	20	-0.03	0.885	20	0.02	0.949	20	0.09	0.694	19	0.23	0.347
6	17	0.54	0.026	20	0.58	0.007	20	0.71	<0.001	20	0.74	<0.001	18	0.67	0.002
7	27	0.30	0.135	34	0.37	0.030	34	0.53	0.001	34	0.41	0.015	28	0.41	0.033
8	107	0.32	<0.001	127	0.21	0.016	127	0.38	<0.001	127	0.29	<0.001	111	0.47	<0.001
9	24	0.40	0.050	27	0.46	0.017	27	0.49	0.009	27	0.37	0.055	25	0.57	0.003
10	13	0.64	0.019	14	0.01	0.386	14	0.58	0.029	14	0.27	0.347	14	0.62	0.019
11	7	0.70	0.062	10	0.39	0.270	10	0.35	0.324	10	0.19	0.593	7	0.51	0.243
12	20	0.66	0.002	25	0.43	0.033	25	0.42	0.035	25	0.46	0.022	21	0.60	0.001
13	22	0.45	0.034	30	0.58	0.001	30	0.73	<0.001	30	0.71	<0.001	24	0.60	0.002
14	90	0.52	<0.001	104	0.45	<0.001	104	0.48	<.0001	104	0.47	<0.001	92	0.55	<0.001
15	26	0.20	0.323	30	0.45	0.013	30	0.48	0.008	30	0.40	0.028	28	0.66	0.001
16	10	0.48	0.159	10	0.60	0.679	10	0.79	0.006	10	0.75	0.013	10	0.86	0.001
17	10	0.58	0.076	10	0.33	0.359	10	0.60	0.066	10	0.54	0.108	10	0.75	0.013
18	14	0.53	0.529	15	0.39	0.156	15	0.55	0.035	15	0.69	0.004	14	0.76	0.001
19	22	0.34	0.119	26	0.25	0.224	26	0.49	0.011	26	0.42	0.033	22	0.62	0.002
20	71	0.32	0.007	80	0.40	<0.001	80	0.39	<0.001	80	0.47	<0.001	73	0.60	<0.001
21	27	0.44	0.021	33	0.34	0.051	33	0.57	<0.001	33	0.51	0.003	29	0.63	<0.001
22	9	-0.17	0.654	12	0.37	0.242	12	0.50	0.099	12	0.33	0.288	10	0.03	0.981
23	4	0.32	0.684	7	0.14	0.757	7	0.16	0.739	7	0.31	0.499	4	0.60	0.400
24	14	0.49	0.076	14	0.12	0.688	14	0.50	0.854	14	0.33	0.232	14	0.40	0.156

Table 3-3: Initial Presentations of Pain and PTSD (*N=288)*

	Worst Pain				Least Pain			
	Coef.	**LCI**	**UCI**	**P - Value**	**Coef.**	**LCI**	**UCI**	**P - Value**
Intercept	1.721	1.317	2.125	< .001	0.039	-0.180	0.258	0.728
Regional Anesthesia								
No	-	-	-	-	-	-	-	-
Yes	-0.393	-0.621	-0.165	0.001	-0.263	-0.396	-0.129	< .001
Month Since Injury (0-24)	-0.031	-0.048	-0.015	< .001	0.001	-0.008	0.011	0.781
Initial PTSD Checklist Score (17-85)	0.020	0.011	0.030	< .001	0.016	0.010	0.022	< .001
Injury Severity Score								
Minor [*Reference*]	-	-	-	-	-	-	-	-
Moderate	-0.060	-0.363	0.244	0.700	0.130	-0.048	0.308	0.153
Serious	-0.060	-0.365	0.246	0.702	-0.013	-0.191	0.166	0.891
Severe	0.071	-0.287	0.429	0.698	0.041	-0.168	0.249	0.701
Length of Hospitalization (Days)	0.006	0.002	0.010	0.007	0.002	0.000	0.005	0.059
Marital Status								
Single [*Reference*]	-	-	-	-	-	-	-	-
Married/Partnered	0.364	0.140	0.588	0.001	0.059	-0.072	0.189	0.378
Separated/Divorced	0.249	-0.218	0.717	0.296	-0.183	-0.455	0.090	0.189
Entry Cohort								
≤ 6 Months [*Reference*]	-	-	-	-	-	-	-	-
6 Months ≤ 1 Year	-0.129	-0.526	0.268	0.524	-0.039	-0.273	0.195	0.745
> 1 Year	1.010	0.335	1.685	0.003	0.476	0.075	0.876	0.020
First Pain Measure	0.577	0.530	0.624	< .001	0.538	0.492	0.585	< .001

Coeff = coefficient; UCI = upper 95% confidence interval; LCI = lower 95% confidence interval; RA = regional anesthesia; BPI = brief pain inventory; PTSD = post-traumatic stress disorder; Initial pain presentation score= the same, initial BPI score corresponding to the outcome measure

Table 3-3 (continued)

	Average Pain				Pain Right Now				Pain Interference			
	Coef.	**LCI**	**UCI**	**P - Value**	**Coef.**	**LCI**	**UCI**	**P - Value**	**Coef.**	**LCI**	**UCI**	**P - Value**
Intercept	0.864	0.584	1.144	< .001	0.129	-0.187	0.445	0.425	-0.160	-0.461	0.141	0.298
Regional Anesthesia												
No	-	-	-	-	-	-	-	-	-	-	-	-
Yes	-0.373	-0.541	-0.205	< .001	-0.274	-0.468	-0.080	0.006	-0.056	-0.237	0.126	0.549
Month Since Injury (0-24)	-0.028	-0.040	-0.016	< .001	-0.019	-0.034	-0.004	0.013	-0.040	-0.053	-0.027	< .001
Initial PTSD Checklist Score (17-85)	0.020	0.013	0.027	< .001	0.027	0.019	0.035	< .001	0.039	0.031	0.047	< .001
Injury Severity Score												
Minor [*Reference*]	-	-	-	-	-	-	-	-	-	-	-	-
Moderate	-0.079	-0.302	0.145	0.491	-0.168	-0.425	0.089	0.199	0.133	-0.109	0.375	0.281
Serious	-0.059	-0.284	0.166	0.608	-0.037	-0.295	0.221	0.778	-0.049	-0.292	0.194	0.693
Severe	-0.066	-0.328	0.197	0.624	-0.219	-0.522	0.084	0.157	0.076	-0.209	0.360	0.601
Length of Hospitalization (Days)	0.003	0.000	0.006	0.037	0.003	-0.001	0.006	0.140	0.006	0.002	0.009	0.001
Marital Status												
Single [*Reference*]	-	-	-	-	-	-	-	-	-	-	-	-
Married/Partnered	0.158	-0.009	0.324	0.064	0.211	0.019	0.404	0.032	0.499	0.321	0.677	< .001
Separated/Divorced	0.060	-0.283	0.403	0.731	-0.039	-0.433	0.356	0.847	0.650	0.279	1.022	0.001
Entry Cohort												
≤ 6 Months [*Reference*]	-	-	-	-	-	-	-	-	-	-	-	-
6 Months ≤ 1 Year	0.143	-0.151	0.436	0.340	0.252	-0.111	0.616	0.174	0.025	-0.289	0.338	0.877
> 1 Year	0.674	0.176	1.172	0.008	0.629	0.005	1.253	0.048	0.518	-0.015	1.050	0.057
First Pain Measure	0.545	0.498	0.593	< .001	0.556	0.509	0.603	< .001	0.485	0.443	0.527	< .001

Coeff = coefficient; UCI = upper confidence interval; LCI = lower confidence interval; RA = regional anesthesia; BPI = brief pain inventory; PTSD = post-traumatic stress disorder; Initial pain presentation score= the same, initial BPI score corresponding to the outcome measure

Table 3-4: Mixed Effects Model with PTSD Trajectory (*N=288*)

	Worst Pain				Least Pain			
	Coef.	LCI	UCI	P - Value	Coef.	LCI	UCI	P - Value
Intercept	2.172	1.797	2.548	< .001	0.344	0.152	0.535	< .001
Regional Anesthesia								
No [*Reference*]	-	-	-	-	-	-	-	-
Yes	-0.353	-0.582	-0.125	0.002	-0.253	-0.387	-0.119	< .001
Month Since Injury (0-24)	-0.030	-0.047	-0.014	< .001	0.002	-0.008	0.012	0.663
Change in PTSD Slope								
Improving (↓) [*Reference*]	-	-	-	-	-	-	-	-
Stable (↔)	-0.384	-0.767	-0.002	0.049	0.039	-0.187	0.264	0.736
Worsening (↑)	-0.039	-0.273	0.195	0.746	0.113	-0.022	0.247	0.100
Injury Severity								
Minor [*Reference*]	-	-	-	-	-	-	-	-
Moderate	-0.034	-0.338	0.270	0.825	0.162	-0.017	0.341	0.077
Serious	-0.042	-0.348	0.263	0.786	-0.004	-0.183	0.176	0.968
Severe	0.032	-0.328	0.392	0.860	0.005	-0.205	0.216	0.961
Length of Hospitalization (Days)	0.006	0.001	0.010	0.010	0.002	0.000	0.005	0.047
Marital Status								
Single [*Reference*]	-	-	-	-	-	-	-	-
Married/Partnered	0.331	0.104	0.559	0.004	0.059	-0.075	0.192	0.388
Separated/Divorced	0.321	-0.148	0.790	0.180	-0.145	-0.420	0.130	0.302
Entry Cohort								
≤ 6 Months [*Reference*]	-	-	-	-	-	-	-	-
6 Months ≤ 1 Year	-0.099	-0.495	0.296	0.623	-0.012	-0.246	0.223	0.923
> 1 Year	1.067	0.387	1.746	0.002	0.566	0.162	0.971	0.006
First Pain Measure	0.607	0.560	0.654	< .001	0.577	0.533	0.622	< .001

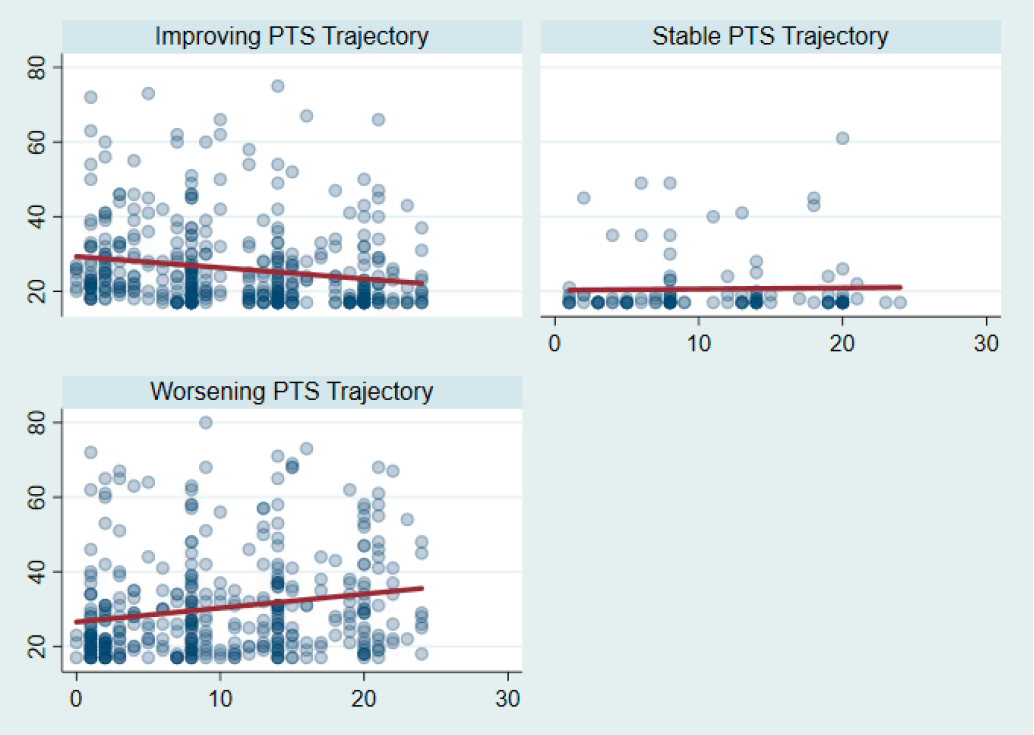
Coeff = coefficient; UCI = upper confidence interval; LCI = lower confidence interval; RA = regional anesthesia; BPI = brief pain inventory; PTSD = post-traumatic stress disorder; Initial pain presentation score= the same, initial BPI score corresponding to the outcome measure

Table 3-4 (continued)

	Average Pain				Pain Right Now				Interference			
	Coef.	LCI	UCI	P-Value	Coef.	LCI	UCI	P-Value	Coef.	LCI	UCI	P-Value
Intercept	1.230	0.977	1.483	< .001	0.582	0.308	0.857	< .001	0.790	0.525	1.054	< .001
Regional Anesthesia												
No [*Reference*]	-	-	-	-	-	-	-	-	-	-	-	-
Yes	-0.343	-0.511	-0.175	< .001	-0.274	-0.471	-0.078	0.006	0.037	-0.149	0.224	0.694
Month Since Injury (0-24)	-0.027	-0.039	-0.015	< .001	-0.017	-0.032	-0.002	0.031	-0.037	-0.051	-0.024	< .001
Change in PTSD Slope												
Improving (↓) [*Reference*]	-	-	-	-	-	-	-	-	-	-	-	-
Stable (↔)	-0.192	-0.474	0.089	0.180	0.145	-0.187	0.476	0.393	-0.511	-0.822	-0.200	0.001
Worsening (↑)	0.203	0.034	0.371	0.018	0.373	0.180	0.567	< .001	-0.064	-0.252	0.124	0.504
Injury Severity												
Minor [*Reference*]	-	-	-	-	-	-	-	-	-	-	-	-
Moderate	-0.045	-0.269	0.178	0.690	-0.130	-0.390	0.129	0.324	0.148	-0.099	0.396	0.241
Serious	-0.049	-0.274	0.175	0.666	-0.028	-0.288	0.232	0.833	-0.054	-0.302	0.194	0.670
Severe	-0.125	-0.388	0.138	0.350	-0.303	-0.608	0.003	0.052	-0.064	-0.355	0.227	0.667
Length of Hospitalization (Days)	0.003	0.000	0.006	0.037	0.003	-0.001	0.007	0.134	0.005	0.002	0.009	0.002
Marital Status												
Single [*Reference*]	-	-	-	-	-	-	-	-	-	-	-	-
Married/Partnered	0.116	-0.053	0.285	0.179	0.201	0.004	0.398	0.046	0.456	0.271	0.641	< .001
Separated/Divorced	0.089	-0.255	0.433	0.612	-0.007	-0.406	0.392	0.972	0.766	0.385	1.147	< .001
Entry Cohort												
≤ 6 Months [*Reference*]	-	-	-	-	-	-	-	-	-	-	-	-
6 Months ≤ 1 Year	0.191	-0.100	0.482	0.198	0.307	-0.057	0.672	0.099	0.099	-0.221	0.419	0.544
> 1 Year	0.741	0.241	1.240	0.004	0.740	0.106	1.375	0.022	0.547	-0.004	1.097	0.052
First Pain Measure	0.581	0.535	0.626	< .001	0.588	0.542	0.634	< .001	0.578	0.539	0.617	< .001

Coeff = coefficient; UCI = upper confidence interval; LCI = lower confidence interval; RA = regional anesthesia; BPI = brief pain inventory; PTSD = post-traumatic stress disorder; Initial pain presentation score= the same, initial BPI score corresponding to the outcome measure

Figure 3-1: PTSD Symptom Trajectories based on PCL-M Slope, examples



PTSD severity (Y Axis) by time of observation since injury (X Axis) with fitted least squares slope of symptom trajectory

PTSD Symptom Trajectories	Last Observed PCL-M Score	First Observed PCL-M Score	Slope	Indicator Term
PTSD Gets Worse	30	17	Positive (+)	Worsening PTSD
PTSD Remains Stagnant	20	20	Zero (0)	Stable PTSD
PTSD Improves	17	30	Negative (-)	Improving PTSD

Figure 3-2: Worst Pain by RA receipt

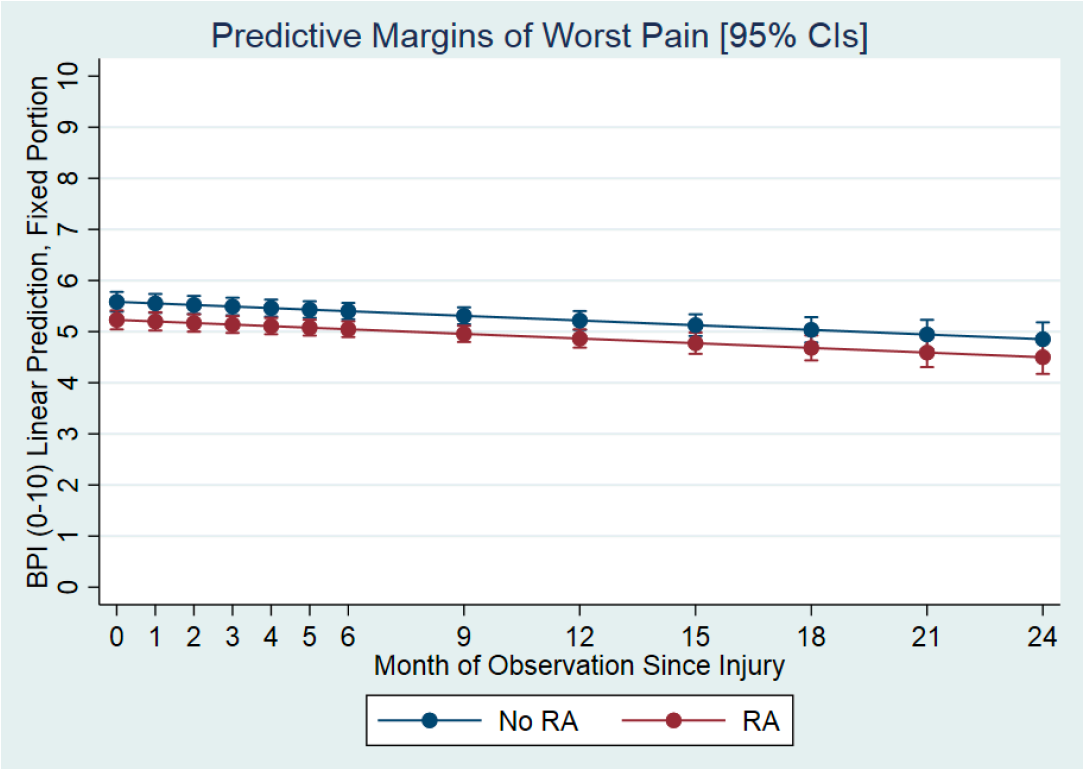


Figure 3-3: Least Pain by RA receipt

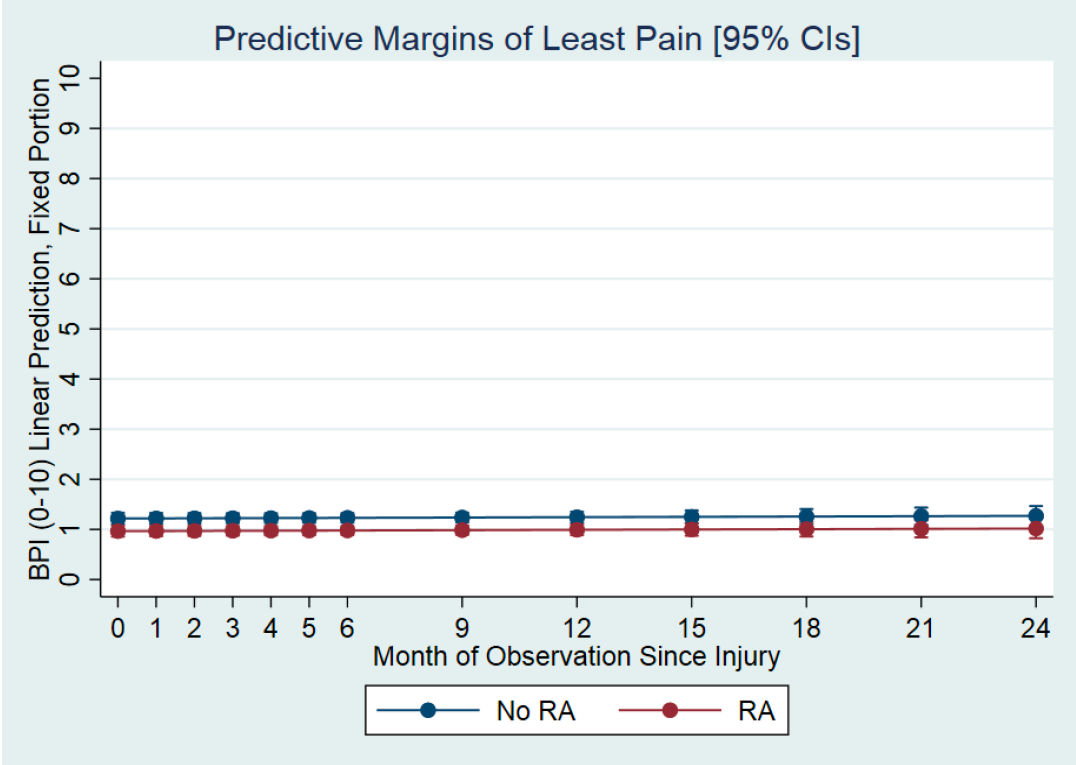


Figure 3-4: Average Pain by RA receipt

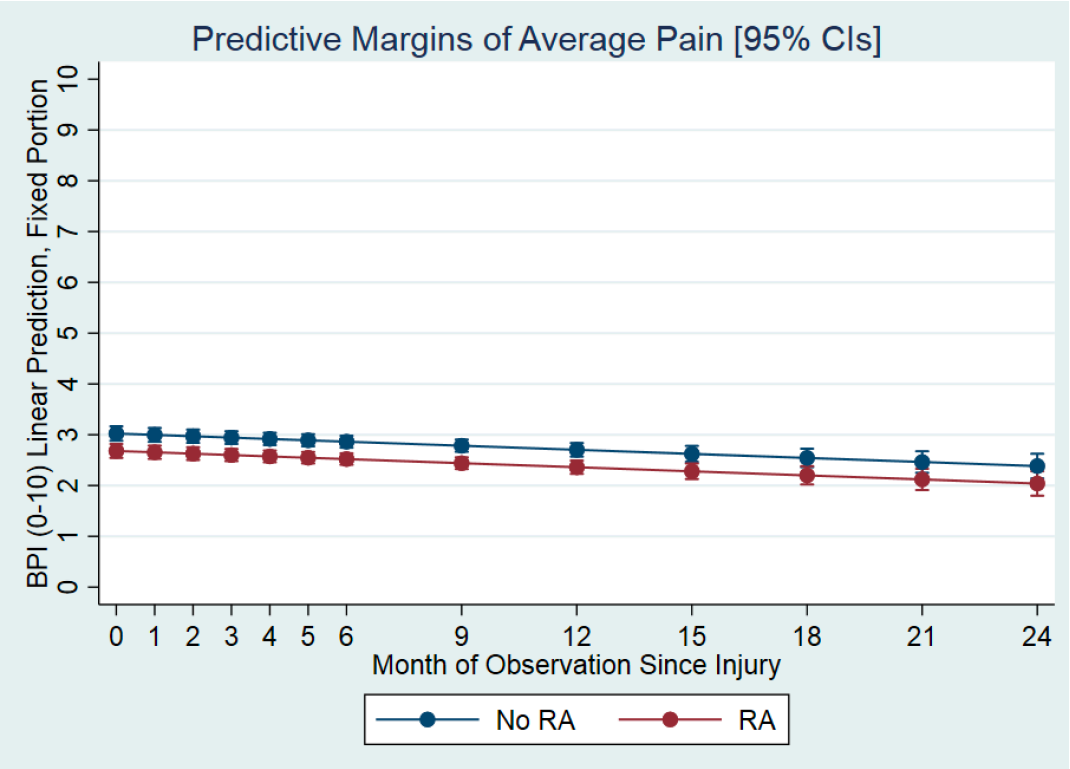


Figure 3-5: Pain Right Now by RA receipt

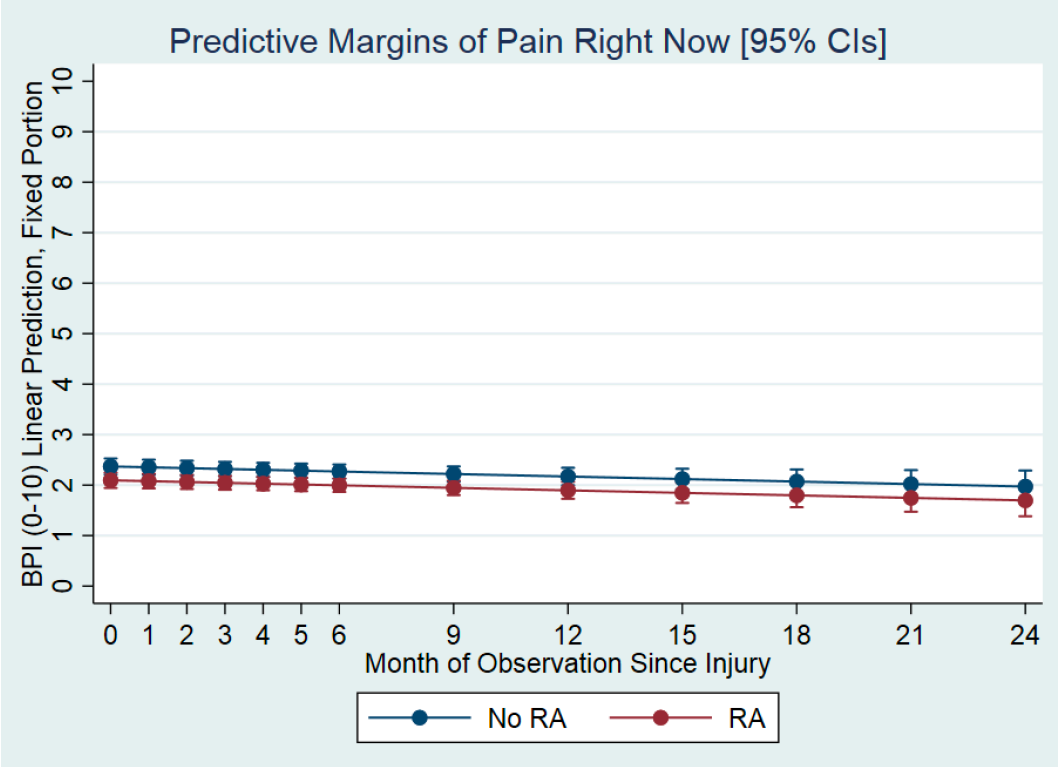


Figure 3-6: Pain Interference by RA receipt

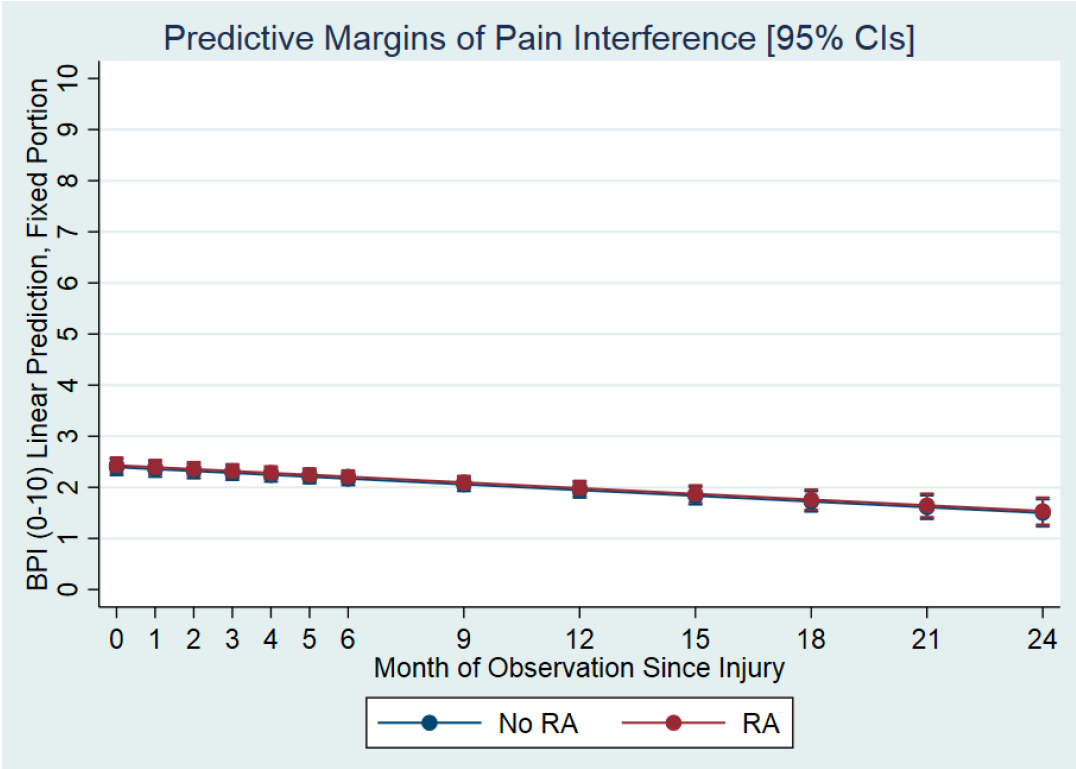


Figure 3-7: Worst Pain by PTSD Symptom Trajectory

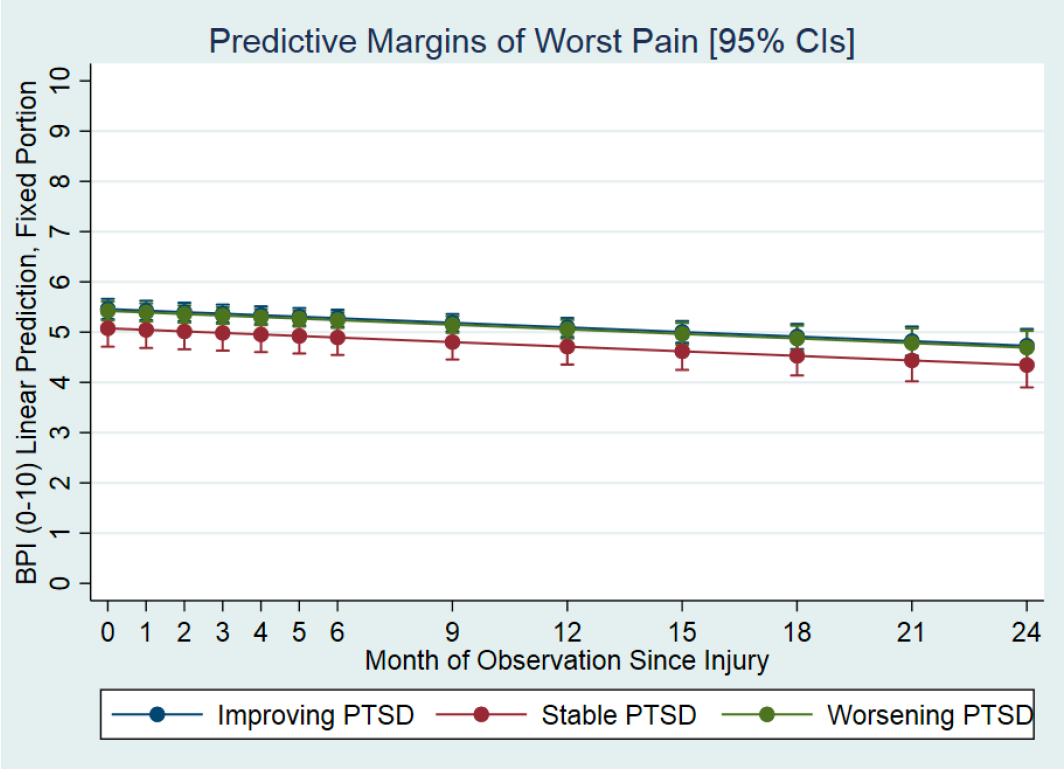


Figure 3-8: Least Pain by PTSD Symptom Trajectory

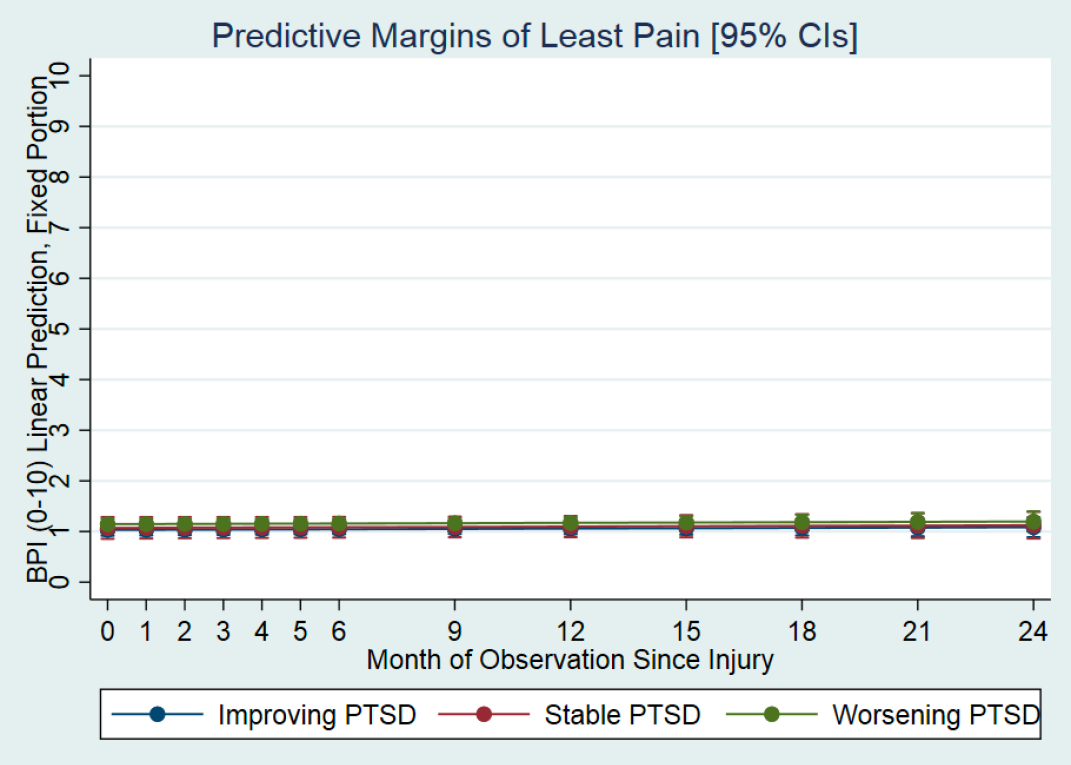


Figure 3-9: Average Pain by PTSD Symptom Trajectory

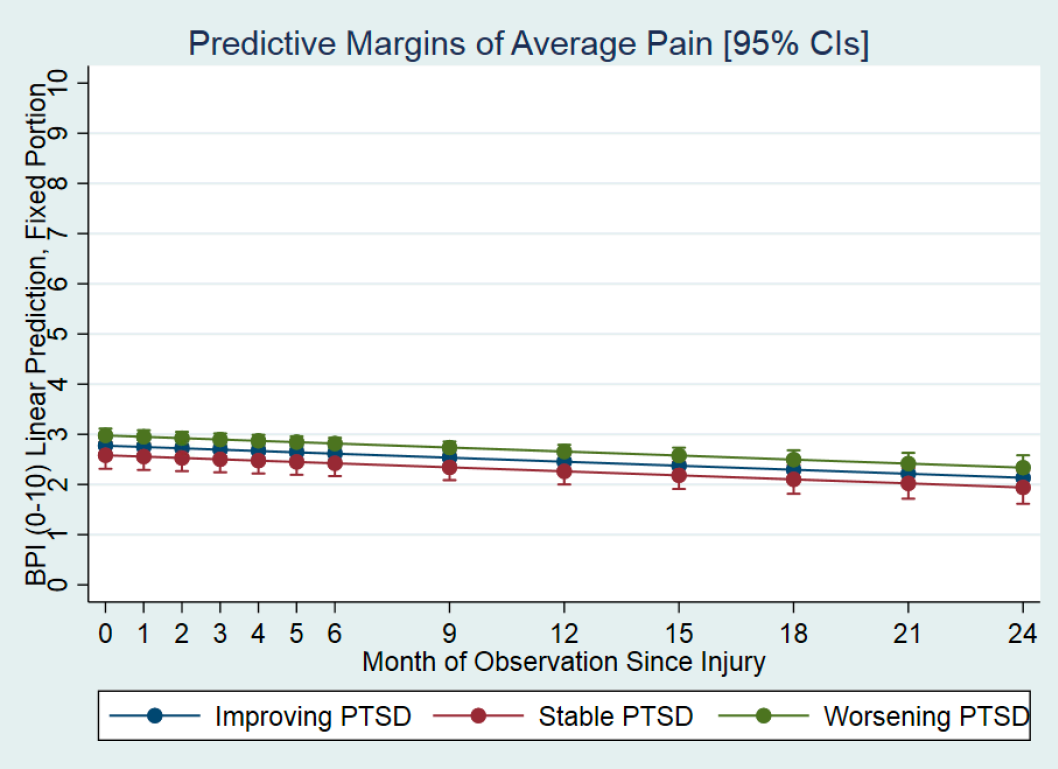


Figure 3-10: Pain Right Now by PTSD Symptom Trajectory

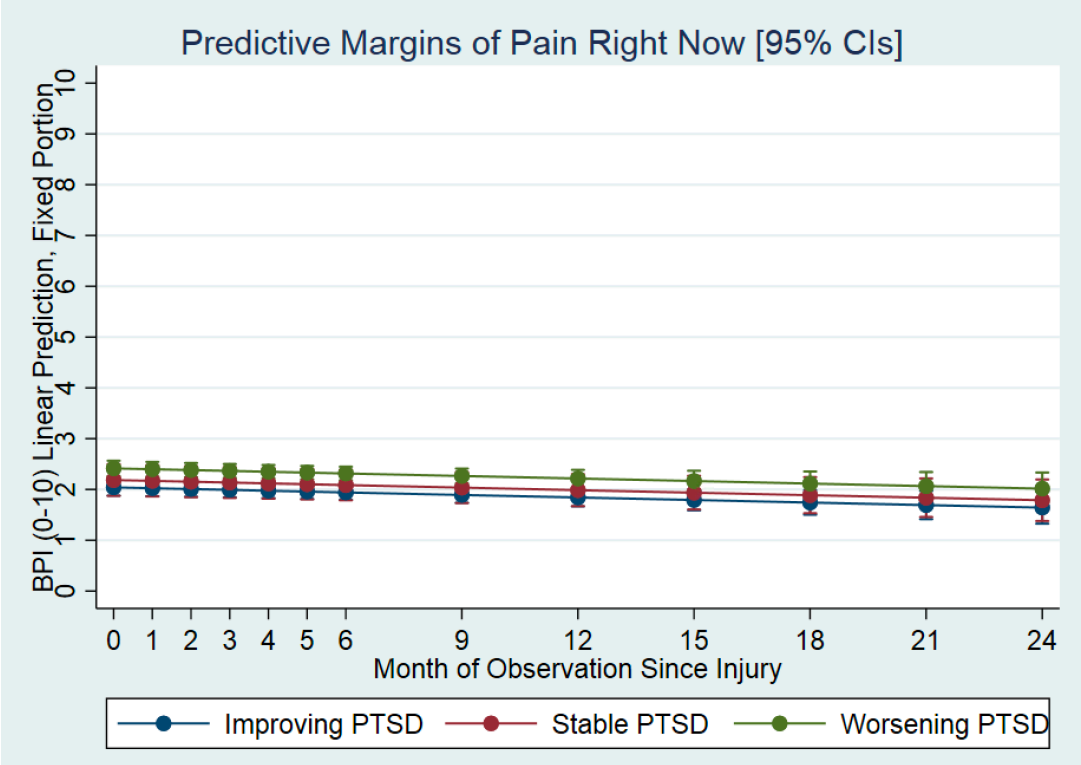
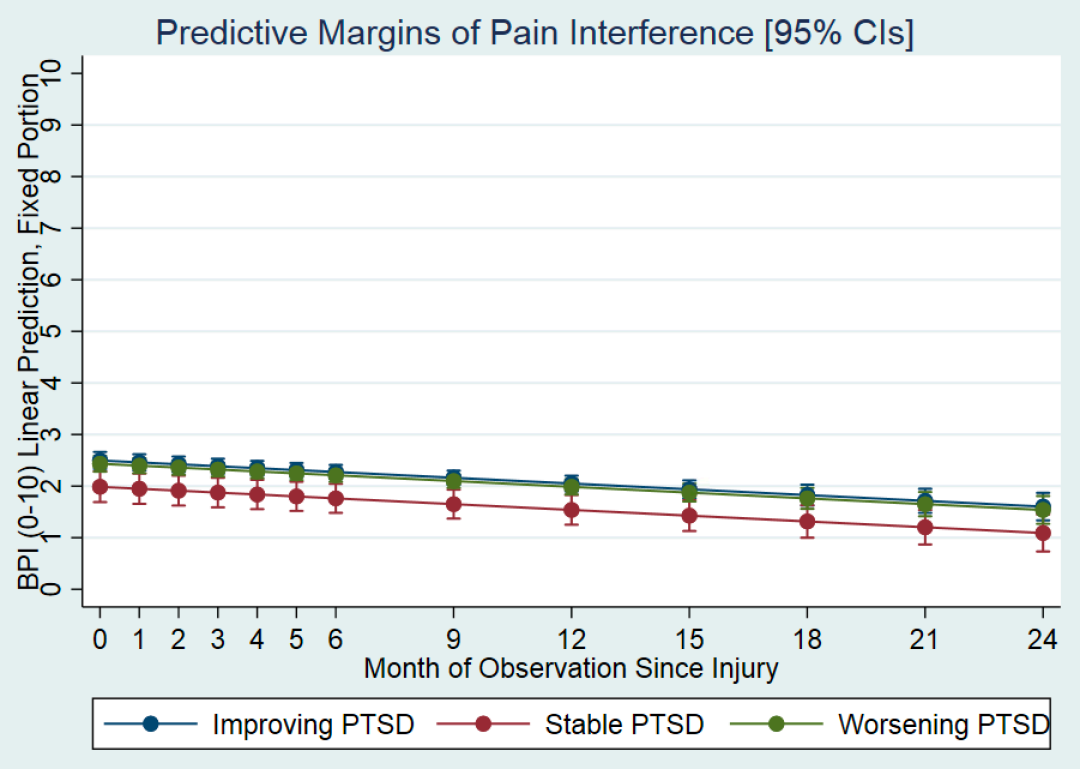


Figure 3-11: Pain Interference by PTSD Symptom Trajectory



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Appendix

Table A3-1: Participant Observation Distributions

Observation #	Participants N=288	Percent
2	26	9.03
3	32	11.11
4	35	12.15
5	26	9.03
6	35	12.15
7	35	12.15
8	28	9.72
9	23	7.99
10	32	11.11
11	10	3.47
12	6	2.08

Table A3-2 Sensitivity Analysis with Adjusted PTSD Trajectory Caliber

	Worst Pain				Least Pain				Average Pain				Pain Right Now				Pain Interference			
	Coef	LCI	UCI	P	Coef	LCI	UCI	P	Coef	LCI	UCI	P	Coef	LCI	UCI	P	Coef	LCI	UCI	P
Intercept	1.88	1.49	2.27	0.00	0.40	0.21	0.58	0.00	1.16	0.90	1.41	0.00	0.53	0.27	0.80	0.00	1.05	0.76	1.33	0.00
Regional Anesthesia																				
No [*Reference*]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Yes	-0.15	-0.40	0.10	0.23	-0.21	-0.34	-0.08	0.00	-0.24	-0.41	-0.07	0.01	-0.15	-0.34	0.04	0.11	0.02	-0.17	0.22	0.83
Month Since Injury (0-24)	-0.04	-0.06	-0.03	0.00	0.00	-0.01	0.01	0.50	-0.03	-0.04	-0.02	0.00	-0.01	-0.03	0.00	0.04	-0.04	-0.05	-0.02	0.00
Change in PTSD Slope																				
Improving (↓) [*Reference*] [n=628]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Stable (↔) [n=636]	-0.28	-0.57	0.01	0.06	-0.06	-0.21	0.10	0.48	-0.23	-0.43	-0.03	0.02	-0.06	-0.28	0.16	0.62	-0.52	-0.76	-0.29	0.00
Worsening (↑) [n=645]	0.06	-0.23	0.36	0.68	0.17	0.02	0.31	0.03	0.31	0.11	0.51	0.00	0.44	0.22	0.65	0.00	-0.14	-0.36	0.09	0.23
Injury Severity Score (continuous)	0.00	-0.01	0.01	0.82	-0.01	-0.01	0.00	0.13	0.00	-0.01	0.00	0.34	-0.01	-0.02	0.00	0.02	-0.01	-0.02	0.00	0.21
Length of Hospitalization (Days)	0.01	0.01	0.01	0.00	0.00	0.00	0.01	0.01	0.01	0.00	0.01	0.00	0.00	0.00	0.01	0.03	0.01	0.00	0.01	0.00
Marital Status																				
Single [*Reference*]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Married/Partnered	0.43	0.19	0.68	0.00	0.05	-0.07	0.18	0.43	0.21	0.04	0.37	0.02	0.14	-0.04	0.33	0.14	0.52	0.33	0.71	0.00
Separated/Divorced	0.11	-0.43	0.65	0.70	-0.01	-0.28	0.27	0.96	-0.02	-0.39	0.35	0.92	-0.05	-0.45	0.36	0.83	0.55	0.14	0.96	0.01
Entry Cohort																				
≤ 6 Months [*Reference*]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6 Months ≤ 1 Year	-0.23	-0.68	0.23	0.33	-0.06	-0.29	0.18	0.64	0.08	-0.22	0.39	0.60	0.38	0.02	0.74	0.04	-0.13	-0.47	0.22	0.47
> 1 Year	1.04	0.28	1.80	0.01	0.60	0.21	0.99	0.00	0.72	0.21	1.23	0.01	0.79	0.18	1.40	0.01	0.41	-0.17	0.99	0.17
First Pain Measure	0.59	0.54	0.63	0.00	0.56	0.51	0.60	0.00	0.55	0.50	0.59	0.00	0.59	0.54	0.63	0.00	0.54	0.50	0.59	0.00

Coeff = coefficient; UCI = upper confidence interval; LCI = lower confidence interval; RA = regional anesthesia; P=P-value; BPI = brief pain inventory; PTSD = post-traumatic stress disorder; Initial pain presentation score= the same, initial BPI score corresponding to the outcome measure

Figure A3-1: PTSD Checklist Scores and Worst Pain, by Month of Observation

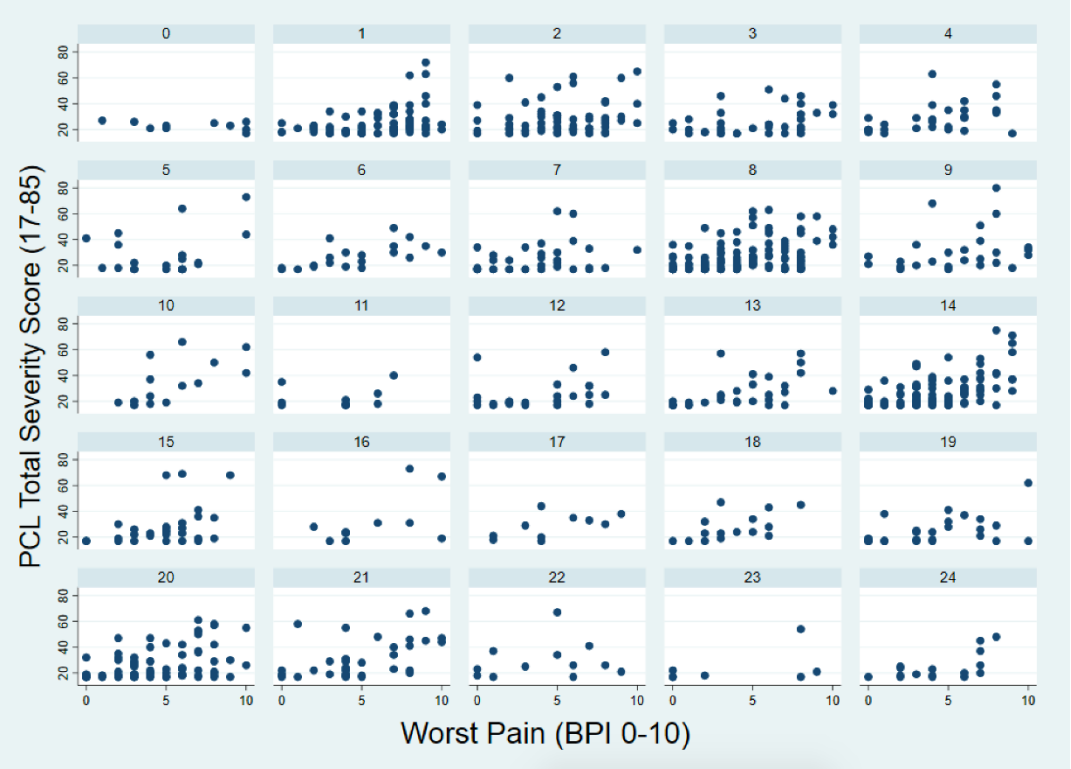


Figure A3-2: PTSD Checklist Scores and Least Pain, by Month of Observation

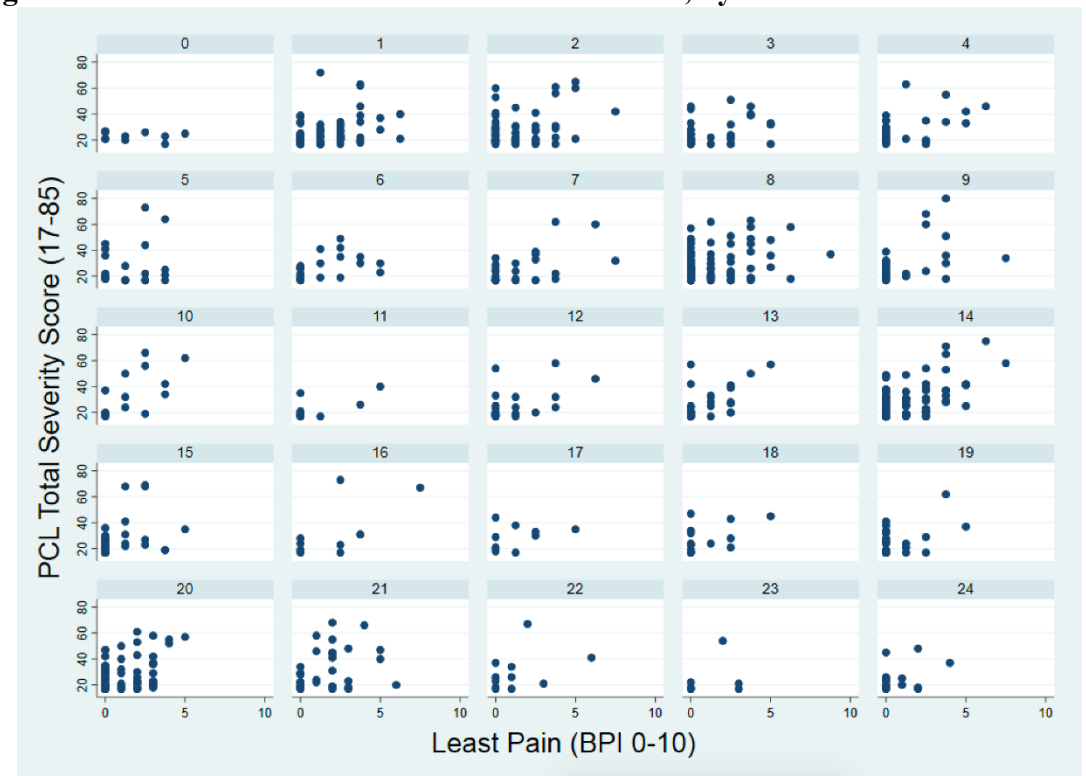


Figure A3-3: PTSD Checklist Scores and Average Pain, by Month of Observation

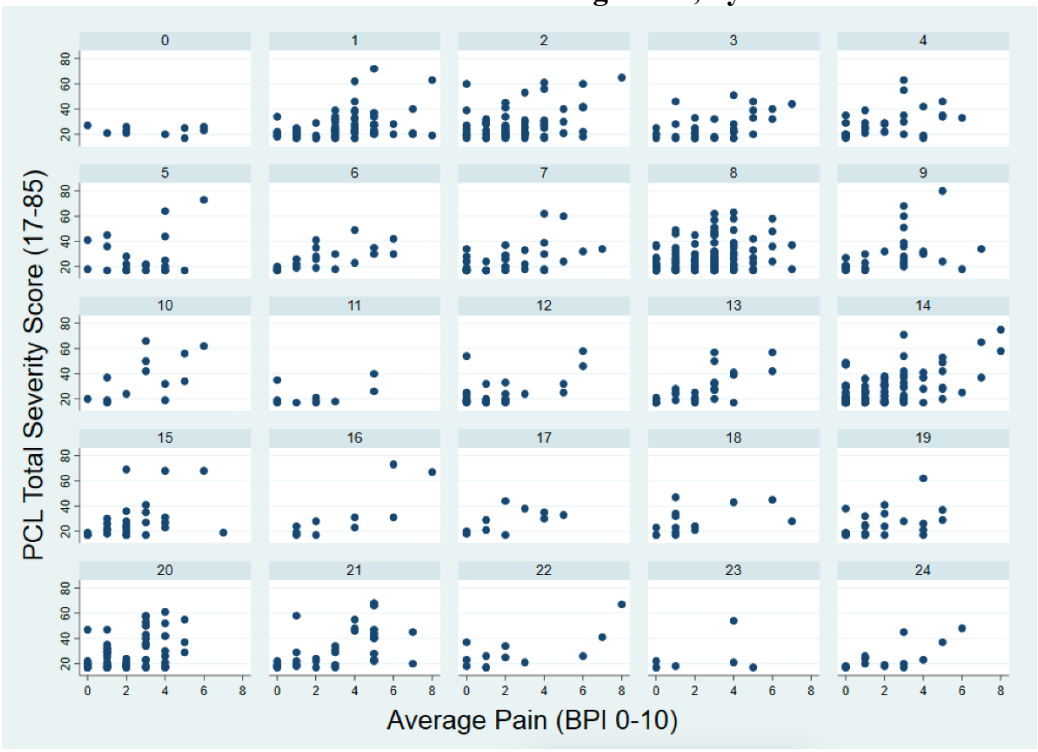


Figure A3-4: PTSD Checklist Scores and Pain Right Now, by Month of Observation

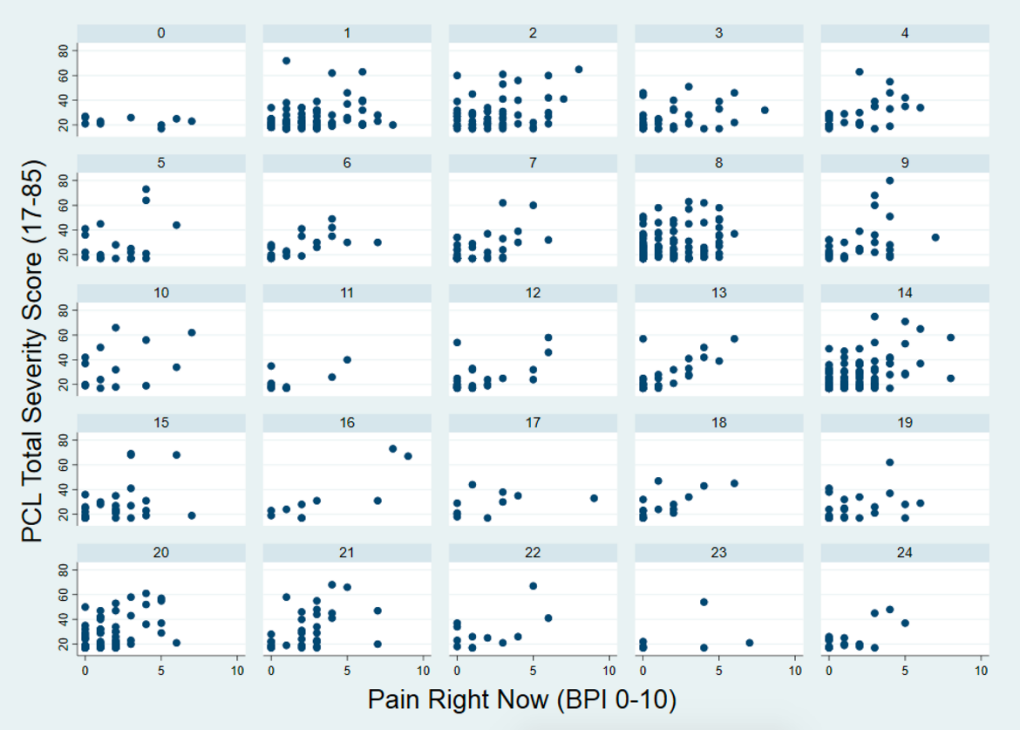
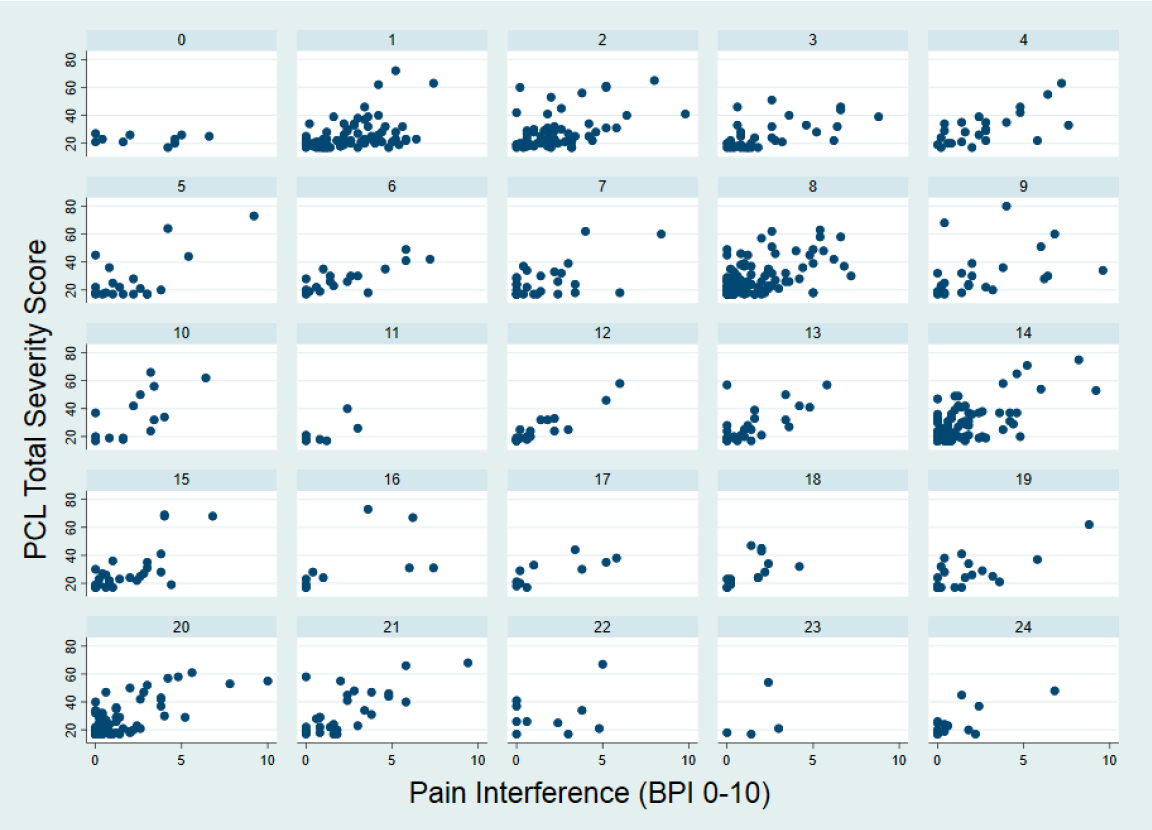


Figure A3-5: PTSD Checklist Scores and Pain Interference, by Month of Observation



CHAPTER 4

Utilizing Markov Models to Illustrate Pain Transitions After Combat Injury

Abstract

Few longitudinal investigations of combat-injured American military personnel and veterans examine the effects of acute pain management on long-term patient-reported pain outcomes. Markov models are mathematical models that can be used to simulate disease process in a series of states, such as describing how patients are likely to transition from one pain state to another, in a probabilistic fashion. Utilizing data from 355 combat-injured military personnel, this modeling study characterized probabilistic pain trajectories, stratified by either receipt of regional anesthesia (RA) or systemic pain management after injury, across multiple dimensions of pain intensity (e.g. worst, average, and pain right now). Findings show that individuals are likely to transition out of states of severe and moderate pain to states of lower pain intensity or no pain. Transition probabilities ranged from <1.00% from no pain to severe pain, to 75.00% for the transition from a state of no pain to remaining in a state of no pain. While simulated projections indicate differences in the probability of remaining in a state of severe or moderate pain up to 24 months after injury by pain management intervention, there is no statistically significant difference between the distributions by regional anesthesia (RA) and standard systemic pain management approaches (worst pain, AD=0.2576, P=0.13; average pain, AD=0.2348, P=0.21; pain right now, AD=0.1853, P=.82). Results indicate that Markov modeling is a practical approach for describing probabilistic combat injury related pain trajectories and can inform care planning beginning from time of acute pain management.

Introduction

Advancements in prehospital combat casualty care have contributed to reducing preventable deaths on the battlefield,[1] but have resulted in soldiers surviving with more severe disabilities and significant problems with chronic pain. Yet, there is a dearth of evidence regarding the long-term benefits of early pain management for survivors. Ongoing pain assessment and management from the point of injury and throughout the care continuum are thought to be key to mitigating risks for developing chronic pain.[2] Despite resolution of the initial injury, maladaptive biopsychosocial mechanisms can manifest in chronic pain, defined as persistent pain lasting over three months.[3] Rates of chronic pain in the United States (U.S.) Operation Enduring Freedom and Operation Iraqi Freedom (OEF/OIF) care-seeking veteran population are estimated to be 28% to 47%,[4] and up to 83% among polytrauma survivors (i.e. those with multiple affected body regions and organ systems).[5] Chronic pain experienced by veterans is associated with lower physical function,[6] increased risk of comorbid mental health conditions (e.g. post-traumatic stress disorder [PTSD]),[7] increased healthcare utilization,[8] and poorer quality of life.[9] The administration of multimodal analgesics in prehospital care and prior to surgery is believed to reduce both peripheral and central sensitization caused by injury, thereby lessening the onset of pain windup, a pathological process contributing to the transition of acute to chronic pain.[10-13]

Timely and targeted delivery of pharmacotherapy in the aftermath of combat injury has a demonstrated ability to reduce acute pain intensity.[14] Yet, widespread patient dissatisfaction with pain control after combat injury suggests acute pain management after injury remains an important area of research.[2] Early aggressive multimodal

management of acute pain is essential to minimize the risk of developing chronic pain after combat injury. The administration of systemic analgesics during trauma care has been found to alleviate acute pain in a timely manner and even reduce the risk of developing mental health conditions.[15-17] However, these systemic approaches increase risks for over sedation, respiratory depression, and vasodilation leading to hypotension and additional blood loss,[18] which can be life-threatening adverse events.

Analgesics and anesthetics delivered through a peripheral nerve block or epidural, known as regional anesthesia (RA), have been shown to provide a more optimal management of acute pain at the point of combat injury and throughout acute care in U.S. military medical facilities.[12,13,16,19,20] RA's targeted delivery of multimodal analgesics has lower risk of hypotension and hypoventilation than that seen in systemic medication administration.[18] Implementation of acute pain services, access to RA trained pain providers in combat support hospitals, and adherence to pain management guidelines have been shown to improve pain monitoring and relief after combat injury.[11,16,21] Yet, research designs examining the effects of acute pain management, specifically RA, in the immediate aftermath of combat injury, transportation, and the intraoperative periods, are generally cross-sectional, retrospective, or of limited duration, with many primarily conducted in the acute phase of recovery.[12,13,16,19,20] Evaluation of the long-term effects of acute pain management is complicated due to the limited pain interventions available in the austere environment, suboptimal recording of pain assessment and treatment documentation throughout care, and challenges engaging survivors in research during community reintegration.[2,11,21] Given the complexities in studying outcomes after combat injury, it is difficult to evaluate the longitudinal nature of pain trajectories. The recently

completed Regional Anesthesia Military Battlefield Pain Outcomes Study (RAMBPOS) collected data at multiple time points over the duration of 2 years after combat-related injury and examined the effect of early acute pain management interventions after injury. RAMBPOS participants provided patient-reported outcomes throughout recovery, including measures of multiple presentations, or dimensions, of their pain experience. The multiple dimensions include worst pain, least pain, average pain, and pain right now at time of assessment.

Markov models are mathematical models that can be used to simulate disease process that can be shown as a series of states, and pain trajectories happen to be such a process. Markov modeling simulates randomly changing systems, or disease states, where the future state is independent of the past and only dependent on the current state. This modeling approach can provide insight into disease or condition specific behavior represented based on a set of transitions. Markov models can be used to leverage currently available pain intensity data sources, such as RAMBPOS, in order to generate parameter estimates from which to draw samples of pain trajectories from large theoretical combat-injured cohorts. Markov models are used extensively in cost-effectiveness analyses to longitudinally project the benefits of pain interventions.[22] The key assumption of a Markov model is that transitions between states form a Markov chain. As such, transitions to future states are dependent only on the current state and not on any previous states. Markov chains represent repetitive events and time, such as changes in pain intensity, using probabilities of future transitions. Tighe et al. demonstrated the application of using Markov chains in illustrating acute pain transitions, from no pain to severe pain, after surgery, using a one-dimensional numeric rating scale

from 0 to 10.[23] Additionally, Markov chains have been used to estimate long-term differences in the cost of care for British military amputees after being injured in Afghanistan.[24] To our knowledge, no investigation has evaluated the effects of RA on long-term pain trajectories after combat injury. The Markov chain approach enables the computation of pain trajectories in a probabilistic manner, while also adjusting for acute pain management interventions and time. The aims of this study are to 1) define probabilities of pain trajectories after combat injury across multiple dimensions of pain intensity, 2) stratify pain trajectories by RA receipt, and 3) estimate pain trajectories from high pain intensity to low pain intensity. The benefit of this approach is that simulations with Markov models can form the foundation of decision models that incorporate care decisions and clinical outcomes, such as quality of life and costs in the future.

Methods

This modeling study utilized RAMBPOS participants' data to estimate transition probabilities. IRB approval for this study was provided by the Veteran's Affairs Office of Research and Development and the University of Pennsylvania.

Description of Data

RAMBPOS is a prospective observational cohort study of U.S. OEF/OIF military personnel with major combat-related limb injuries and known receipt status to early aggressive RA. By collecting patient-reported outcomes over the first two years after combat injury, RAMBPOS provides one of the most comprehensive examinations of the short- and long-term benefits of implementing early RA for pain control after major traumatic limb injuries. Depending on the date and geographic location of injury, individuals received RA in two ways, potentially. Either (1) upon arrival at a combat

support hospital in a forward operating base with a trained military RA provider deployed at the time, or (2) based the availability of RA providers and acute pain services upon arrival in a U.S. military hospital. Individuals receiving RA within two weeks after injury in either of these conditions are part of the RA cohort. The No RA cohort consists of participants who did not receive early RA within two months of injury. The No RA cohort received standard systemic multimodal pain management throughout transportation and acute care at U.S. military medical facilities.

The RAMBPOS dataset includes patient demographics, injury characteristics, RA treatment and patient-reported pain outcomes. Participants were recruited and consented during acute care and rehabilitation at two military medical facilities in the continental U.S. Any military personnel with a combat-related major injury involving one or more extremities and requiring hospitalization was eligible for enrollment. Eligible individuals with cognitive deficits, moderate and severe traumatic brain injury (TBI), inability to concentrate, poor judgment and impulse control, substantial hearing loss, and bilateral upper extremity amputation with no alternate means to complete the survey forms were excluded. After eligibility screening and consent, individuals could enter the study at any time within the first two years after injury. Between October 2007 and September 2014, a total of 386 individuals were enrolled. Medical records in the Department of Defense (DOD) Trauma Registry, provided clinical and military career information, including injury characteristics, sociodemographic information, and RA receipt status. Patient-reported outcomes, including the Brief Pain Inventory (BPI), were collected monthly within the first 6 months after injury and every 3 months after, up to 24 months after

combat injury. Only participants with two or more complete BPI observations were included in this analysis, for a total of 355 eligible participants.

The Brief Pain Inventory (BPI) is a 9-item pain assessment tool measuring pain intensity and interference.[25,26] The BPI measures the multidimensional nature of pain intensity, specifically worst pain, average pain, and pain right now. Worst pain refers to the most intense pain experienced in the past 24 hours, measured from 0, "no pain" 10, "pain as bad as you can imagine." The BPI average pain measure is an individual's reflection of the routine pain they experienced in the past 24 hours, whereas pain right now refers to pain experienced at time of assessment using the same 0 to 10 scale. Leading experts from the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) panel recommended that all measures of pain intensity, rather than just current pain, be included as outcomes in chronic-pain clinical trials.[27] The BPI was chosen for the analysis because of its brevity, its capability to capture multiple dimensions of pain intensity, and its frequency of administration in the parent study. For each BPI pain intensity score, the time since injury (measured in months) was calculated to create a common reference point. Using 3-subscales of the BPI (worst pain, average pain, and pain right now), we defined 4 pain states: no pain, mild pain, moderate pain, and severe pain (**Figure 4-1**). These states correspond to established pain intensity classifications from BPI scores: none (0), mild (1-4), moderate (5-6), and severe (7-10).[28] This categorization by pain intensity rating was compared to an expanded multiple objective state categorization utilizing the 0 to 10 BPI responses. The utility of the expanded form in long-term clinical care and medical decision-making is questionable, and therefore, the four-pain state approach was determined to be best for this analysis.

Pain state is defined by an individuals' BPI pain intensity (e.g., average, worst, and pain right now) scores at any given month after injury. The transition from one pain state to another (even if remaining in a specific state) over time, refers to individuals' changes in BPI pain intensity scores. These transitions, when examined over time, are considered the pain trajectory. Individuals can only be in one pain state, over one discrete time period, per trajectory. However, across pain trajectories individuals can be in different pain states (e.g. in severe worst pain at one month and in mild average pain during that same month). The RAMBPOS' BPI data were used to obtain the probability of transitioning between each pain state for patients receiving RA compared to No RA. In total, three pain trajectories were constructed and then stratified by RA receipt status. The BPI measure for least pain was excluded from the modeling after assessing distribution was almost exclusively a score of 0 or 1.

Defining the Markov Chains and Transition Matrices

Markov models are mathematical predictions of recursive decision trees that are used to model conditions with events that may occur repeatedly over time, such as pain intensity. Markov models explicitly account for the passing of time, in the case of this analysis each month since injury, and values of pain intensity at designated time points throughout the study. Pain intensity values are discrete and measurements occur at regular intervals which is a criterion for modeling as a stochastic process, using Markov chains. In terms of Markov chains, future transitions are based on the present state of an individual and are independent of past transitions or states.[29] An individual's history of BPI score derived pain states does not influence their next or future transitions in this analysis.

Collectively, the pain states and their associated probabilities in Markov chains are presented as a transition matrix.

The transition matrix provides insight as to how combat-injured individuals move across pain states in a probabilistic manner. In the transition matrix, the rows represent the current state of the individual, and the columns represent future states. Using a long file, with separate records for each repeated measure by a RAMBPOS participant, individuals' monthly movements from one pain state to another were counted using an algorithm. Probability parameters were derived by summing the total transition count (the number of time transitions) from one pain state (row) to an another (column), all divided over the sum of the row's count. One of the goals of acute pain management is to move patients from a state of high pain intensity to a state of lower intensity. A prolonged length of stay, up to three months, in a state of high pain intensity (moderate or severe) were considered chronic pain for the purpose of this analysis. Transitions were modeled in monthly increments. The Markov chain allows for the evaluation of movement across states in a series of steps by multiplying the probability of moving from a row specified state by the probability of a column state raised to the number of months. Stationary distributions derived from the Markov chain probabilities allow for side by side comparison between stratified groups, such as RA and No RA. Similarly, the number of transitions needed, or time in which individuals move from high pain intensity to low pain intensity states can be compared.

Results

Overall, RAMBPOS participants were young (28.00 years old, [Standard Deviation] +/- 7.1), male (99.20%), non-Hispanic (87.40%) and white (77.50%) (**Table 4-1**). Injury

severity was measured using the Injury Severity Score (ISS), a numeric rating scale where 75 indicates the greatest severity and death, and 0 is equal to no injury. More than half the sample experienced serious (32.6%) or severe injuries (22.70%), with an average injury severity score of 18.40 (+/- 10.8). Length of acute hospitalization was about 37 days, on average (+/- 33.4). The average number of deployments in this sample was 2 (+/- 1.3). In this subsample, 185 participants received RA, and 170 did not, known as the No RA group. Three quarters of participants entered the RAMBPOS ≤ 6 months after injury (75.80%). **Table 4-2** provides sample characteristics of the RAMBPOS participant's pain transition data used for this analysis. In total, 2,214 pain observations provided from 355 participants were used to calculate transition probabilities. About half of the observations were from participants who had received RA (51.90%) and the other half from those who did not receive RA (48.10%).

Overview of the Transition Matrices

The value of condensing pain states from 11 discrete states (0 to 10), to 4 (none, mild, moderate, severe) is that movement across states requires larger incremental changes in pain intensity and is not as sensitive to small, and less clinically meaningful, changes. The condensed states, using worst pain as an example, provides an observable trend in transition probabilities. The worst pain transition matrix is positive recurrent and irreducible with no absorbing state. Individuals can transition from any pain state to another, with a probability as low as 1.00% and as high as 65.00% (**Figure 4-2**). The strongest probabilities are individuals transitioning from their current state and remaining there, with a probability of 49.00% to 65.00% (i.e. the diagonal of the table). However, in the average pain matrix individuals are rarely in a state of severe pain and remain there

with probabilities from 0.00% to 8.0% (**Figure 4-3**). Similarly, individuals in severe pain right now infrequently remain in a state of severe pain (probabilities 0.00% to 16.00%). In the pain right now matrix, individuals have a higher probability to quickly transition from severe to moderate pain states (43.00%) and from moderate to mild pain states (59.00%). This indicates individuals gravitate towards lower pain states when reporting pain right now.

Characterization of Stationary Distributions by RA

Transition matrices for worst pain, average pain, and pain right now were stratified by intervention status (RA vs. No RA). Initial distributions across pain states by RA status are displayed **Table 4-3**. Initial distributions are provided by the RAMBPOS cohorts and their clinical pain presentations in the study. **Figure 4-4** compares the stationary distribution for worst pain by RA and No RA. There was no statistically significant difference in the distributions by intervention (Anderson-Darling [AD] = 0.2576, P = 0.13). Based on the initial distribution provided by the RAMBPOS, after two years, or 24 monthly transitions, there is a 18.60% probability that individuals who did not receive early RA will be in state of no pain, 28.90% in a state mild pain, 38.00% in moderate pain, and 14.5% severe pain. Alternatively, there is only a 10.10% probability for those who receive early RA to be in a state of no pain, 30.60% in a state in mild pain, 45.40% in moderate pain, and 13.90% in severe pain (**Figure 4-5**).

The distributions were not statistically different by RA status, both for average pain and pain right now (AD = 0.238, P = 0.21; AD = 0.1853, P > 0.82, respectively). Based on the transition matrix for average pain (**Figure 4-6**) individuals receiving RA have a probability estimate of 24.10% to be in no pain, 56.90% in mild pain, 18.40% in

moderate pain, and only 0.60% in severe pain up to 2 years after injury. Overall, individuals who do not receive RA have a probability of 28.70% to be in no pain, 47.80% in mild pain, 23.20% in moderate pain, and 0.39% in severe pain (**Figure 4-7**). The transition matrices for pain right now (**Figure 4-8**) indicate a probability of 35.30% in no pain, 55.00% in mild pain, 8.70% in moderate pain, and only 1.00% in severe pain at 24 months post-injury and after receiving RA after 24 months (**Figure 4-9**). Alternatively, a larger probability exists for individuals not receiving RA to be in no pain right now, 44.80%, but also a slightly larger probability to be in severe pain, 2.30%. At 2 years after injury individuals without RA have a 46.90% probability of being in mild pain right now and 6.00% in moderate pain right now.

The most prominent transition occurs within the first 6 months after injury and provides an opportunity to examine the movement from severe acute pain to no pain (**Figures 4-10, 4-11, 4-12**). For example, if all combat-injured individuals (100% of a given sample) are assumed to be in severe average pain within the first month after injury, there is a 58.70% probability that combat-injured persons receiving RA are estimated to transition to mild or no pain within 3 months. Whereas, only a 52.70% probability for individuals not receiving RA to be in average mild or no pain in that same transition time of 3 months. This translates to less than a quarter (23.90%) of RA recipients being in chronic moderate or severe average pain at 6 months, compared to a third (30.70%) of individuals who did not receive RA. This projection can continue out to 24 months, for participants who did receive RA the probability of remaining in chronic moderate or severe pain is less than a fifth (19.00%) as opposed to a 23.00% probability among participants not receiving early RA. However, this trend of RA individuals

transitioning out of severe or moderate pain faster does not hold for pain right now. A higher proportion of individuals who received RA remain in chronic moderate or severe pain at 3 months (18.40%, RA; 15.70%, No RA), 6 months (11.50% RA; 9.60% No RA), or 24 months (10.80% RA; 8.30% No RA). There is a slightly smaller estimated probability for RA recipients to experience moderate or severe worst pain (72.40%) than those without early aggressive RA (73.30%) in the first 3 months after injury. Yet, there is a higher probability for individuals receiving early RA to experience moderate or severe worst pain at 6 months (62.20%) and 24 months (59.30%) in comparison to the No RA cohort (59.90%, 6 months; 52.50%, 24 months).

Discussion

The findings of this study demonstrate how individuals move across pain states after combat injury using Markov chains to visualize the transition from moderate and severe acute pain to moderate and severe chronic pain. Early pain trajectories, in the initial months after injury, have the potential to inform researchers and providers of individuals likely to develop future chronic severe or moderate pain.[30] These trajectories can inform the proactive and timely delivery of acute pain management interventions that not only control pain but also prevent long-term moderate or severe chronic pain from developing. Modeling symptom trajectories and responses to management interventions can inform the design of future pragmatic trials that utilize successful interventions. The utility of the Markov chain approach can be seen in the use of projecting possible clinical pain presentations after combat injury. For this evaluation Markov chains modeled pain state transitions by both initial presentations of the true RAMBPOS sample as well as generating estimates based on proposed initial clinical presentations. For the latter,

simulations were based on the assumption that all participants in a hypothetical combat-injured population present with severe pain within the first month after injury. In these projections individuals in severe average pain or pain right now quickly transition to lower pain intensity states within 3 and 6 months after injury. However, there is probability that individuals, both those receiving RA and No RA, remain in chronic severe or moderate average pain up to two years after severe injury. This sustained absorption and steady proportion of individuals in the higher pain intensity states highlight the need for continued assessment and management of all combat-injured veterans.

Acute pain trajectories have been used as predictors of the future development for chronic pain after acute tissue trauma, such as surgery. Others have examined the utility of linearly predicting acute pain, specifically following surgery, but are limited to a few days or months at a time and do not evaluate the long-term nature of chronic pain transitions.[30-32] Similar to other analyses of pain trajectories, the findings of this study confirm the general improvement of pain intensity over time.[30,31,33,34] However, improvements are not necessarily linear in nature as proposed in the past. Understanding pain trajectories with higher precision than what simple linear fits are able to provide, are needed.[30] Markov models allow the characterization of individual's pain trajectories through transition states and thereby able to identify abnormal acute pain resolutions. These unaddressed abnormal resolutions can present as stable prolonged time spent in moderate or severe chronic pain after 3 to 6 months. Tighe et al.'s probabilistic Markov chains demonstrate the utility of stratifying patients into risk groups for increased pain intensity based on their clinical characteristics.[23] Despite their larger sample size (N=

476,108), the author's do not account for pain management interventions patients receive. Althaus et al. followed patients up to six months after surgery to project long-term transitions from acute to chronic pain, but again did not consider initial acute pain interventions. This analysis uniquely evaluated pain trajectories after combat injury stratified by RA status using a probabilistic approach. Additionally, this evaluation offers an overview of the longitudinal transitions of pain across multidimensional pain outcomes (e.g. worst pain, average pain, and pain right now), unlike other analyses that are limited to only acute post-operative pain trajectories and current pain intensity presentations.

Longitudinal studies examining pain trajectories over weeks and months after early pain management are important in order to describe how pain changes as severe physical injuries resolve.[35] This lack of literature may be due, in part, to the inherently unpredictable nature of trauma and the focus of controlling pain rather than preventing pain from occurring.[36] Studies examining severely injured civilian populations have reported that pain can affect individuals up to 36 months after injury.[37] Moreover, elevated pain intensity immediately after injury is strongly associated with chronic pain in civilian populations with lower extremity injures.[35] The retrospective nature of much of this body of injury and pain trajectory research emphasizes the need for prospective studies. This probabilistic modeling provides a possible means by which to illustrate pain trajectories utilizing existing pain data sources from clinical trials, such as RAMBPOS, and health records.

In this secondary analysis, RA and systemic pain management approaches were shown to be effective in reducing length of time spent in severe and moderate pain after

injury. While differences in probability transitions were found between RA groups, they did not reach statistical significance. RA distributions were not statistically different from No RA probability distributions. RA is an established multimodal pain management intervention demonstrated to improve acute pain, one of the largest risk factors for developing chronic pain, after combat injury in Iraq and Afghanistan.[12,13,16,19] Researchers have confirmed the improvements of RA over systemic analgesics on improving health outcomes after injury.[38-40] Further, a meta-analysis of civilian surgical patients indicated that epidural anesthesia and blocks help prevent chronic postoperative pain up to one year after surgery.[41] Studies examining the benefits of RA in combat injured populations beyond acute care are limited in availability; possibly due to the highly transient nature of military personnel and veterans after discharge as they return to their civilian lives. While there was no statistically significant difference in the probability distributions between RA and No RA, this analysis was the first to demonstrate the utility of using Markov chains to model pain transitions after combat injury in OEF/OIF military personnel and veterans. For example, transition matrices indicate the utility of RA in reducing the proportion of individuals in prolonged severe and moderate pain within a few months after combat injury up to two years later. This work estimates necessary underlying probability parameters to build future Markov models that incorporate utility values for quality of life, and even cost.

Limitations of this analysis include the nature of the clinical data used and the assumptions needed to utilize Markov chains. Despite RAMBPOS being one of the largest and most comprehensive dataset of patient-reported pain outcomes after combat injury, there are a limited number of observations compared to other's analyses of pain

outcomes using Markov models.[23] Given the limited number of observations, transition probabilities for the matrices were evenly populated from observations by RA and No RA cohorts. Future analyses should be conducted on more robust datasets of pain outcomes. Inherent limitations of the Markov chain include assumptions of independence that may defy the true nature of pain. For example, an individual's pain intensity responses may be influenced by their previous pain intensity and therefore not independent to predict future pain intensity. Further, these Markov transitions evaluated differences by RA receipt, and did not consider underlying factors that can influence an individual's pain intensity, such as mental health diagnoses. Approximately a quarter of the data utilized for this analysis were generated by individuals who joined RAMBPOS more than six months after injury. Therefore, it is important to note that those participants joining later have inherently less follow-up time than those enrolled earlier after injury and could have poorer pain outcomes on which average probability transitions were estimated. However, RAMBPOS is one of the first longitudinal studies measuring patient-reported pain outcomes after combat injury and evaluating acute pain management interventions. Therefore, this work is exploratory in nature and provides the parameters for future modeling work in the regards to conducting cost-effectiveness analyses with analgesic interventions. In the future, Bayesian approaches can be incorporated to calibrate model parameters and probabilistic distributions to overcome these limitations if a large enough sample of longitudinal pain intensity measures can be obtained.

Conclusion

In conclusion, the unique features of the Markov model enable evaluation of pain intensity trajectories after combat injury. Moreover, this analysis captured the multidimensional nature of pain intensity, as opposed to a single 0 to 10 assessment of current pain intensity at time of observation. Findings indicate that individuals receiving RA transition quickly out of severe and moderate average pain intensity in the first six months after injury compared to No RA individuals, however, there was no statistically significant difference in the probability distributions. This research provides foundational findings that can be leveraged for future cost-effectiveness analyses, that in turn can contribute to better understanding of the benefits of RA after combat injury.

Figure 4-1: Visualization of the Markov model's pain states (circles) with transition pathways (arrows)

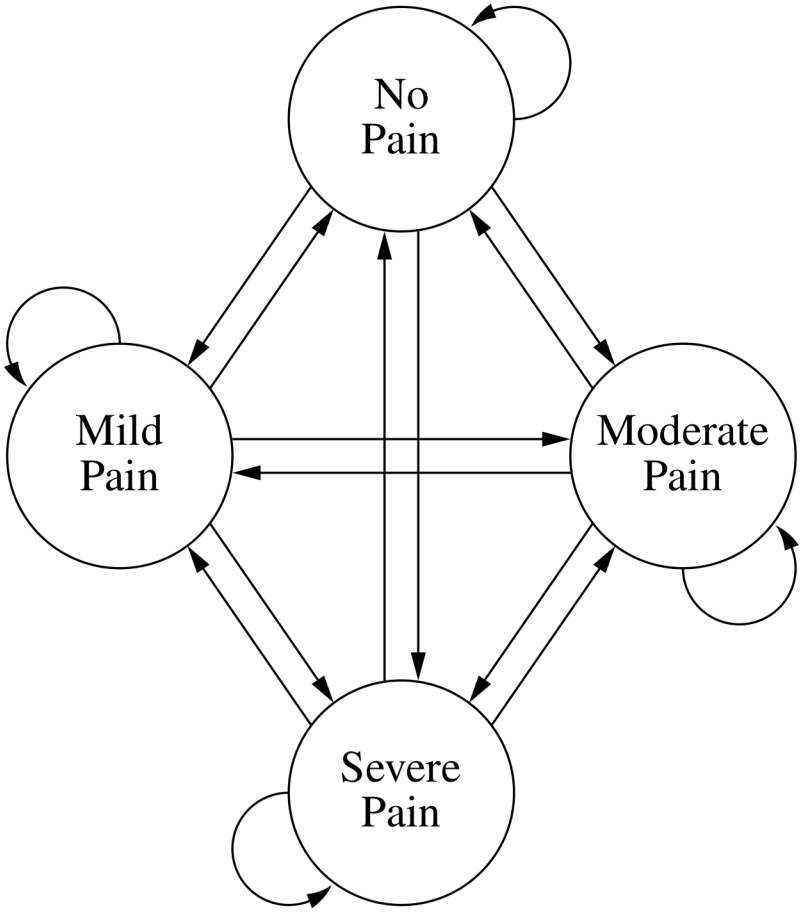


Table 4-1: RAMBPOS Subsample Characteristics

	Total N=355	
Age		
Mean	28	
Std. dev.	7.1	
Number of Deployments		
Mean	2	
Std. dev.	1.3	
Length of Stay in Hospital		
Mean	36.7	
Std. dev.	33.4	
Injury Severity Score		
Mean	18.4	
Std. dev.	10.8	
	%	**N**
ISS Category		
Minor (≤9)	21.20%	75
Moderate (10-15)	23.50%	83
Serious (16-24)	32.60%	116
Severe (≥25)	22.70%	81
Time Since Injury to Entering Study		
≤ 6 Months	75.80%	269
6 Months ≤ 1 Year	14.30%	51
> 1 Year	9.90%	35
Regional Anesthesia		
Yes	52.11%	185
No	47.89%	170
Sex		
Female	0.80%	3
Male	99.20%	352
Race		
White	77.60%	276
Black	5.30%	19
Other	17.10%	60
Ethnicity		
Hispanic	12.60%	44
Non-Hispanic	87.40%	311

Std. dev=standard deviations; ISS= Injury Severity Score; HS= High School

Table 4-2: RAMBPOS Participant Data for Markov Model

Variables	Observations (N=2214)	Percent
Worst Pain (BPI Score)		
None (0)	217	9.8%
Mild (1-4)	865	39.2%
Moderate (5-6)	467	21.1%
Severe (7-10)	665	30.0%
Average Pain (BPI Score)		
None (0)	437	19.8%
Mild (1-4)	1450	65.5%
Moderate (5-6)	270	12.2%
Severe (7-10)	57	2.6%
Pain Right Now (BPI Score)		
None (0)	796	35.9%
Mild (1-4)	1180	53.3%
Moderate (5-6)	184	8.3%
Severe (7-10)	54	2.4%
Regional Anesthesia		
Yes (n=185)	1150	51.9%
No (n=170)	1064	48.1%

BPI=Brief Pain Inventory

Figure 4-2: Illustration of Expanded to Condensed Pain States

Transition Matrix of Post-Injury Worst Pain, 11 States (BPI 0-10) [N=2214]

	0	1	2	3	4	5	6	7	8	9	10
0	0.65	0.15	0.07	0.05	0.03	0.01	0.01	0.01	0.01	0.00	0.01
1	0.25	0.31	0.19	0.11	0.06	0.03	0.01	0.02	0.01	0.01	0.00
2	0.09	0.16	0.23	0.17	0.16	0.05	0.06	0.04	0.02	0.01	0.01
3	0.09	0.09	0.16	0.27	0.18	0.10	0.03	0.05	0.03	0.00	0.00
4	0.05	0.03	0.10	0.25	0.20	0.12	0.12	0.08	0.04	0.01	0.00
5	0.03	0.01	0.06	0.13	0.22	0.20	0.14	0.14	0.05	0.00	0.02
6	0.02	0.02	0.04	0.07	0.15	0.15	0.20	0.17	0.14	0.03	0.01
7	0.01	0.00	0.03	0.06	0.10	0.11	0.15	0.24	0.20	0.06	0.04
8	0.00	0.01	0.03	0.04	0.05	0.10	0.11	0.21	0.30	0.10	0.05
9	0.00	0.00	0.00	0.03	0.03	0.05	0.12	0.17	0.32	0.20	0.08
10	0.02	0.00	0.05	0.02	0.04	0.04	0.14	0.21	0.21	0.11	0.16

Transition Matrix of Post-Injury Worst Pain, 4 States (BPI 0-10) [N=2214]

	No Pain (0)	Mild (1-4)	Moderate (5-6)	Severe (7-10)
No Pain (0)	0.65	0.27	0.07	0.01
Mild (1-4)	0.12	0.55	0.3	0.03
Moderate (5-6)	0.03	0.21	0.61	0.15
Severe (7-10)	0.01	0.06	0.44	0.49

Transition Table Key

Lowest 10% Transition Probabilities				Top 10% Transition Probabilities

BPI = Brief Pain Inventory

Figure 4-3: Transition Matrices of Average Pain and Pain Right Now

Transition Matrix of Post-Injury Average Pain, 4 States BPI (0-10) [N=2214]

	No Pain (0)	Mild (1-4)	Moderate (5-6)	Severe (7-10)
No Pain (0)	0.71	0.27	0.02	0.00
Mild (1-4)	0.14	0.73	0.12	0.00
Moderate (5-6)	0.01	0.32	0.64	0.02
Severe (7-10)	0.00	0.17	0.75	0.08

Transition Matrix of Post-Injury Pain Right Now, 4 States BPI (0-10) [N=2214]

	No Pain (0)	Mild (1-4)	Moderate (5-6)	Severe (7-10)
No Pain (0)	0.75	0.24	0.01	0.00
Mild (1-4)	0.18	0.72	0.08	0.02
Moderate (5-6)	0.06	0.59	0.25	0.10
Severe (7-10)	0.09	0.32	0.43	0.16

BPI = Brief Pain Inventory

Table 4-3: Initial Pain State Distributions from RAMBPOS (N=385)

	Worst Pain		Average Pain		Pain Right Now	
	RA	No RA	RA	No RA	RA	No RA
No Pain	4.8%	9.4%	11.8%	12.9%	25.3%	12.9%
Mild	28.0%	34.7%	68.8%	65.9%	56.5%	65.9%
Moderate	31.7%	18.2%	14.5%	15.9%	12.9%	15.9%
Severe	35.5%	37.6%	4.8%	5.3%	5.4%	5.3%

Figure 4-4: Transition Matrices of Worst Pain, by Regional Anesthesia

Transition Matrix of Post-Injury Worst Pain, for RA, 4 States BPI (0-10) [N=1150]

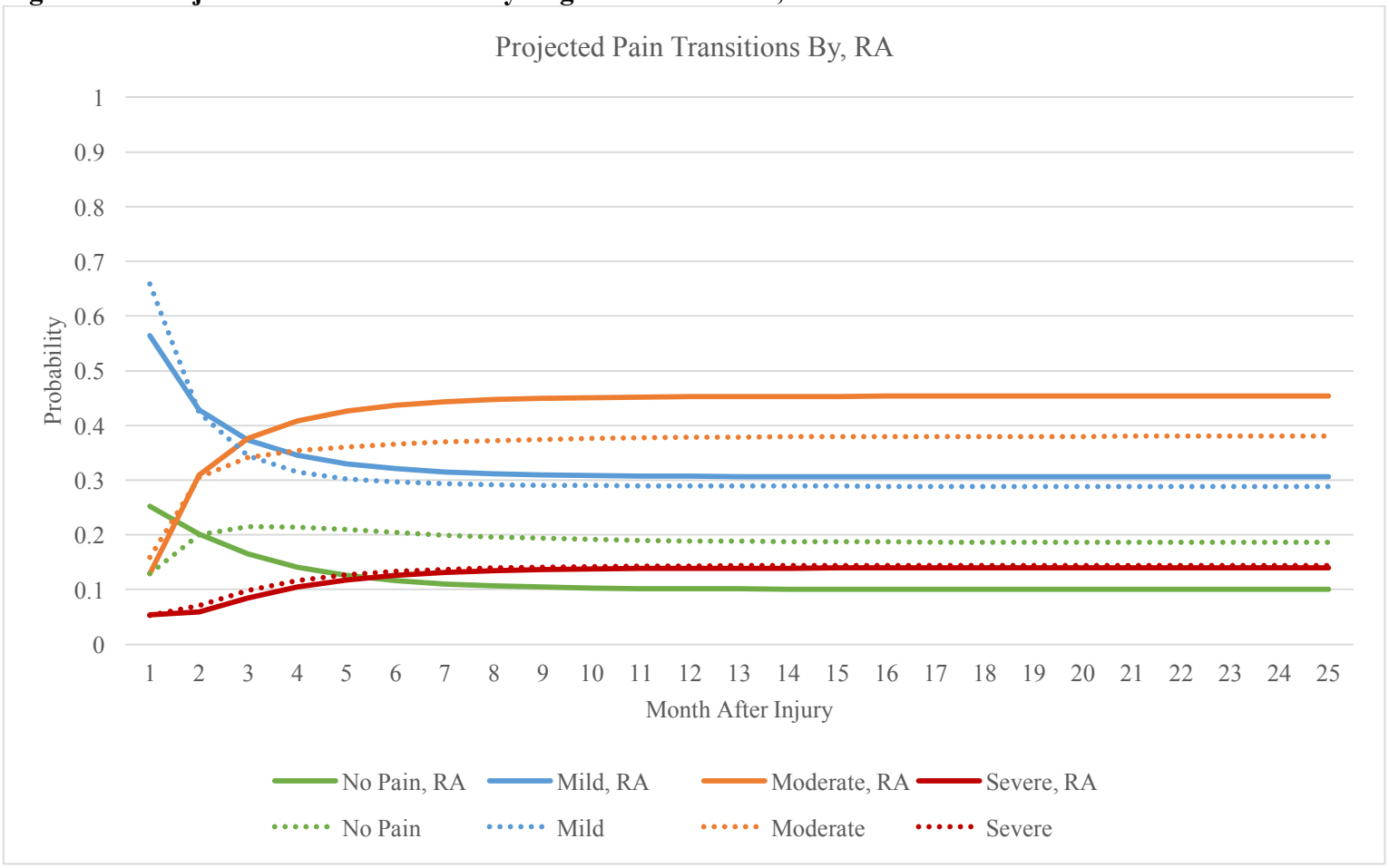
	No Pain (0)	Mild (1-4)	Moderate (5-6)	Severe (7-10)
No Pain (0)	0.58	0.31	0.11	0.00
Mild (1-4)	0.09	0.57	0.31	0.03
Moderate (5-6)	0.03	0.20	0.62	0.15
Severe (7-10)	0.01	0.06	0.46	0.46

Transition Matrix of Post-Injury Worst Pain, for No RA, 4 States BPI (0-10) [N=1064]

	No Pain (0)	Mild (1-4)	Moderate (5-6)	Severe (7-10)
No Pain (0)	0.70	0.24	0.04	0.02
Mild (1-4)	0.16	0.54	0.27	0.02
Moderate (5-6)	0.02	0.21	0.61	0.16
Severe (7-10)	0.01	0.06	0.42	0.52

BPI = Brief Pain Inventory, RA= regional anesthesia

Figure 4-5: Projected Pain Transitions by Regional Anesthesia, Worst Pain



RA= regional anesthesia

Based on distributions in Table 4-3 probability of being in a pain state after 24 monthly transitions, by RA

Figure 4-6: Transition Matrices of Average Pain, by Regional Anesthesia

Transition Matrix of Post-Injury Average Pain, for RA, 4 States BPI (0-10) [N=1150]

	No Pain (0)	Mild (1-4)	Moderate (5-6)	Severe (7-10)
No Pain (0)	0.68	0.31	0.02	0.00
Mild (1-4)	0.13	0.75	0.11	0.00
Moderate (5-6)	0.01	0.37	0.60	0.02
Severe (7-10)	0.00	0.17	0.67	0.17

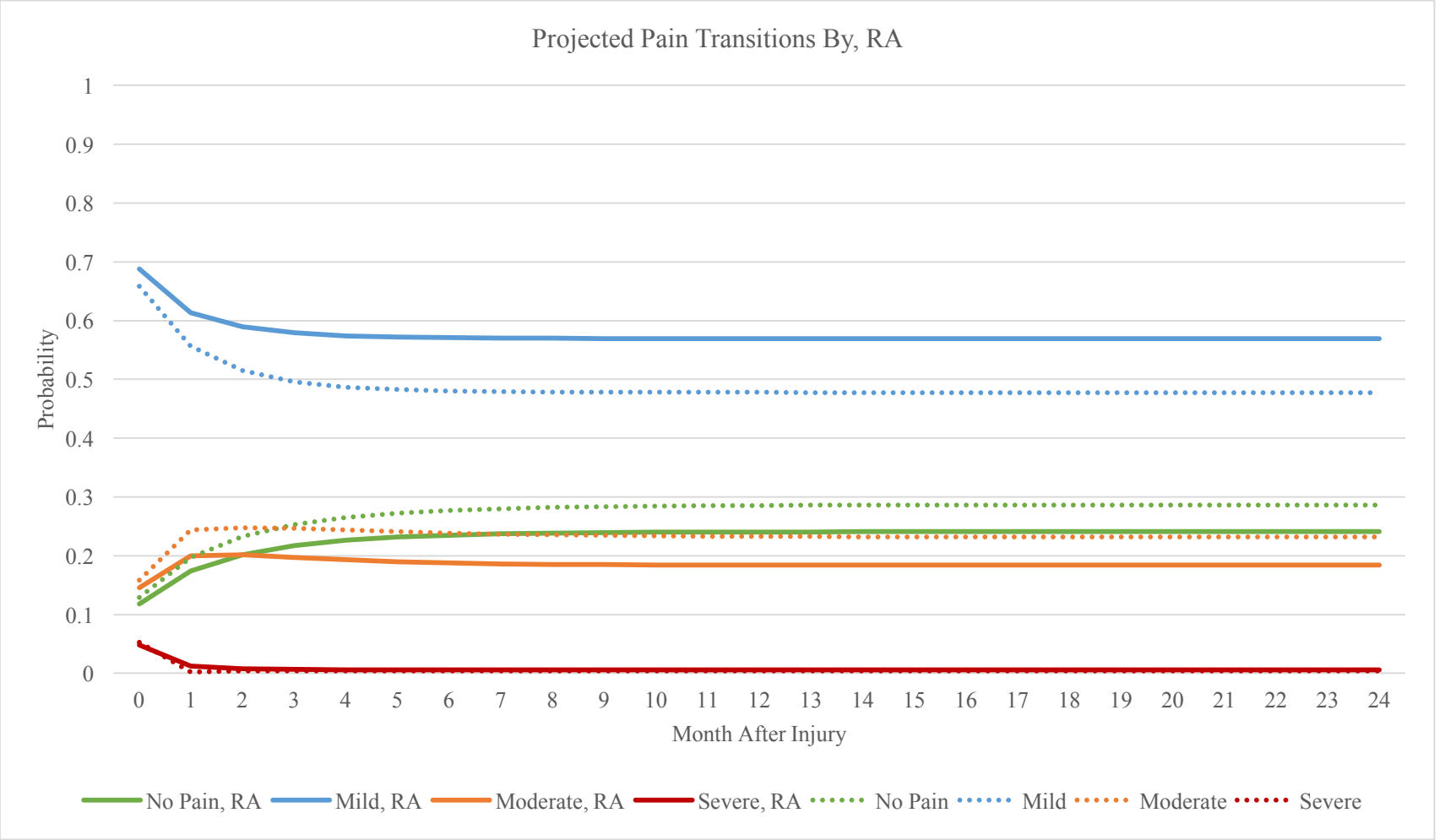
Transition Matrix of Post-Injury Average Pain, for No RA, 4 States BPI (0-10) [N=1064]

	No Pain (0)	Mild (1-4)	Moderate (5-6)	Severe (7-10)
No Pain (0)	0.73	0.24	0.02	0.00
Mild (1-4)	0.15	0.72	0.13	0.00
Moderate (5-6)	0.02	0.28	0.68	0.02
Severe (7-10)	0.00	0.17	0.83	0.00

BPI = Brief Pain Inventory, RA= regional anesthesia

The distributions were statistically equivalent by RA status both for average pain (AD = 0.238, P > 0.05)

Figure 4-7: Projected Pain Transitions by Regional Anesthesia, Average Pain



RA= regional anesthesia

Based on distributions in Table 4-3 probability of being in a pain state after 24 monthly transitions, by RA

Figure 4-8: Transition Matrices of Pain Right Now, by Regional Anesthesia

Transition Matrix of Post-Injury Pain Right Now, for RA, 4 States BPI (0-10) [N=1150]

	No Pain (0)	Mild (1-4)	Moderate (5-6)	Severe (7-10)
No Pain (0)	0.70	0.27	0.02	0.01
Mild (1-4)	0.18	0.72	0.09	0.01
Moderate (5-6)	0.07	0.59	0.25	0.08
Severe (7-10)	0.09	0.26	0.48	0.17

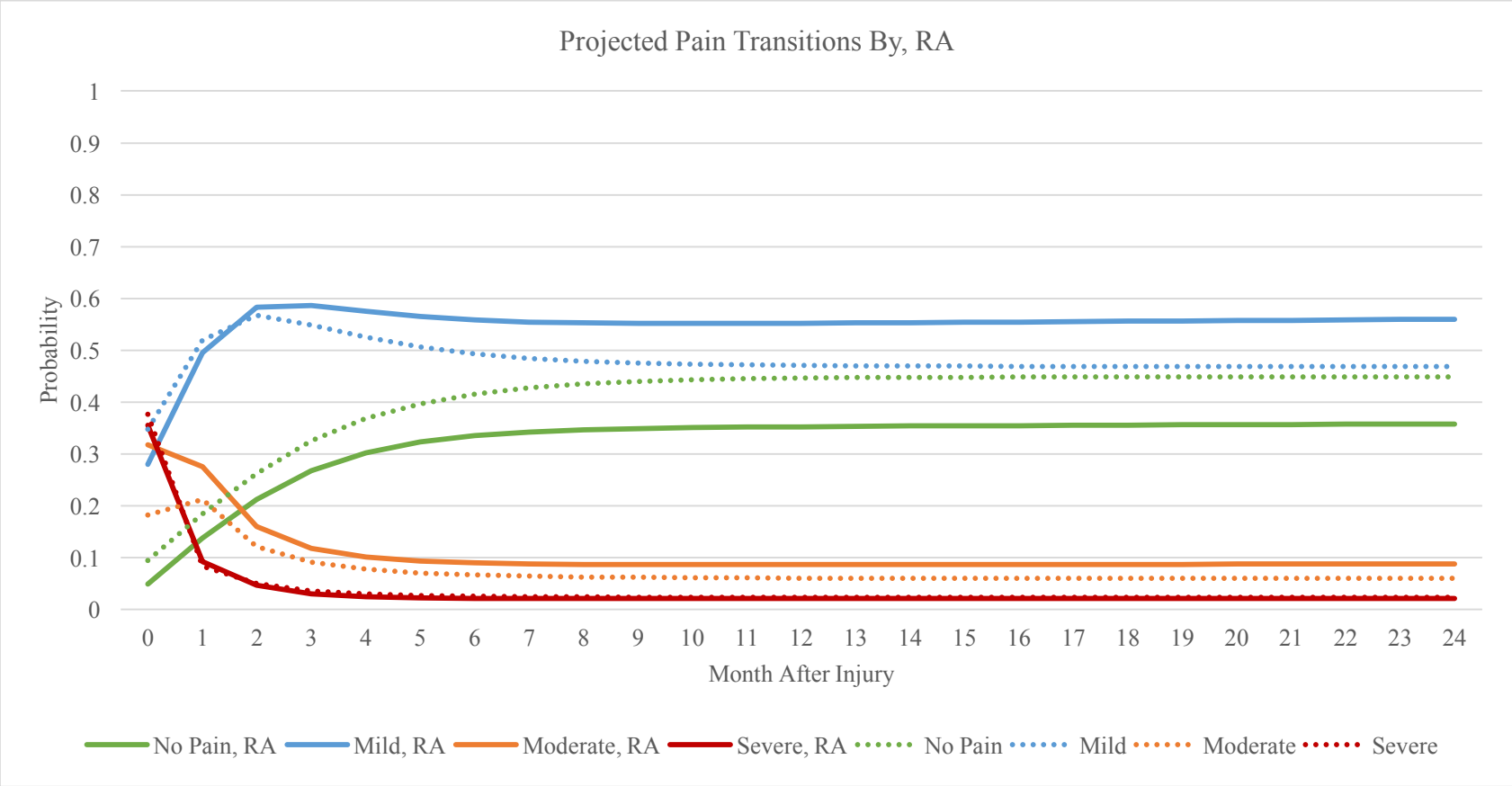
Transition Matrix of Post-Injury Pain Right Now, for No RA, 4 States BPI (0-10) [N=1064]

	No Pain (0)	Mild (1-4)	Moderate (5-6)	Severe (7-10)
No Pain (0)	0.79	0.20	0.01	0.00
Mild (1-4)	0.19	0.71	0.07	0.02
Moderate (5-6)	0.05	0.60	0.23	0.12
Severe (7-10)	0.10	0.38	0.38	0.14

BPI = Brief Pain Inventory, RA= regional anesthesia

The distributions were statistically equivalent by RA status both for pain right now (AD = 0.1853, $P > 0.05$)

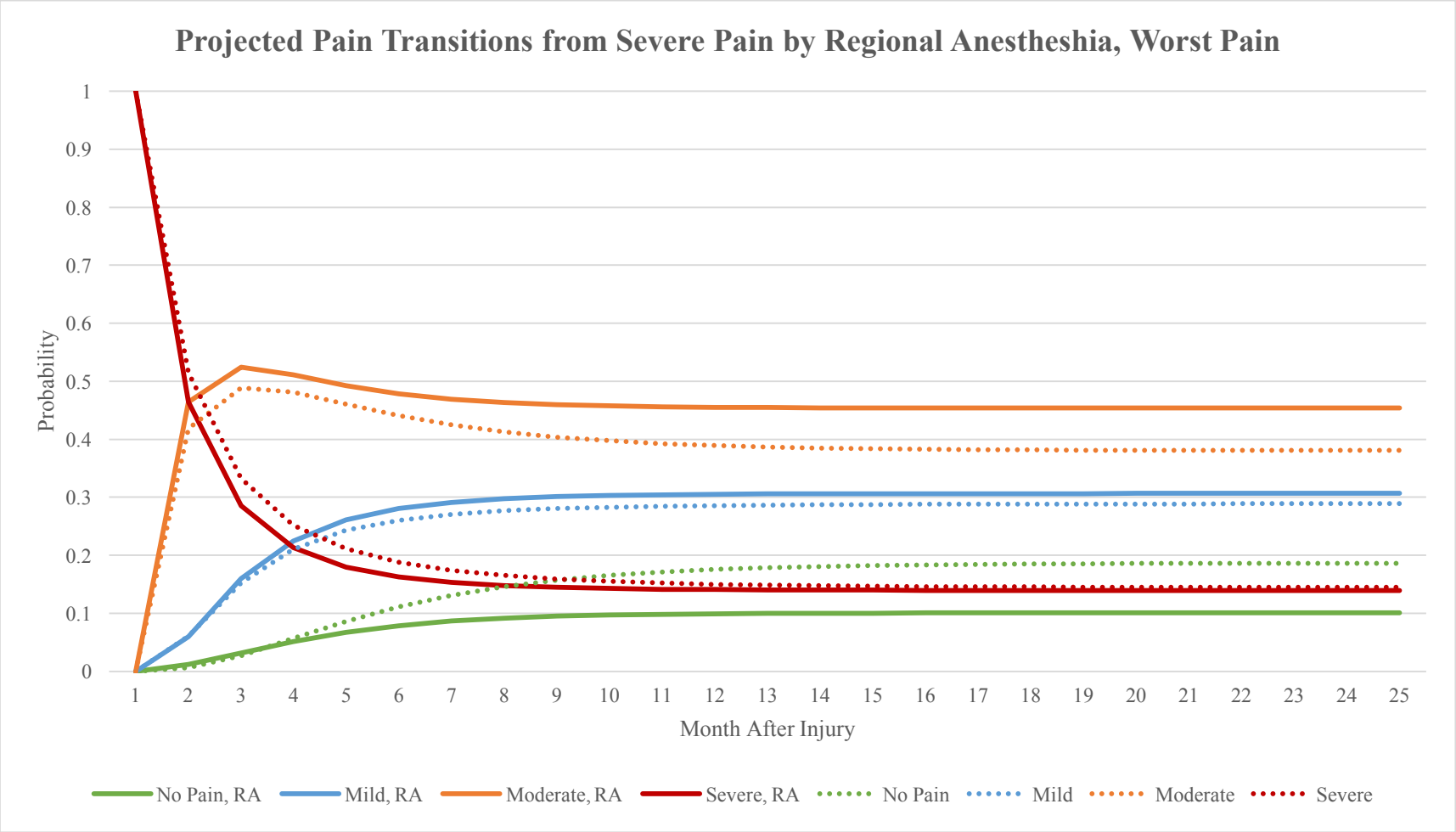
Figure 4-9: Projected Pain Transitions by Regional Anesthesia, Pain Right Now



RA= regional anesthesia

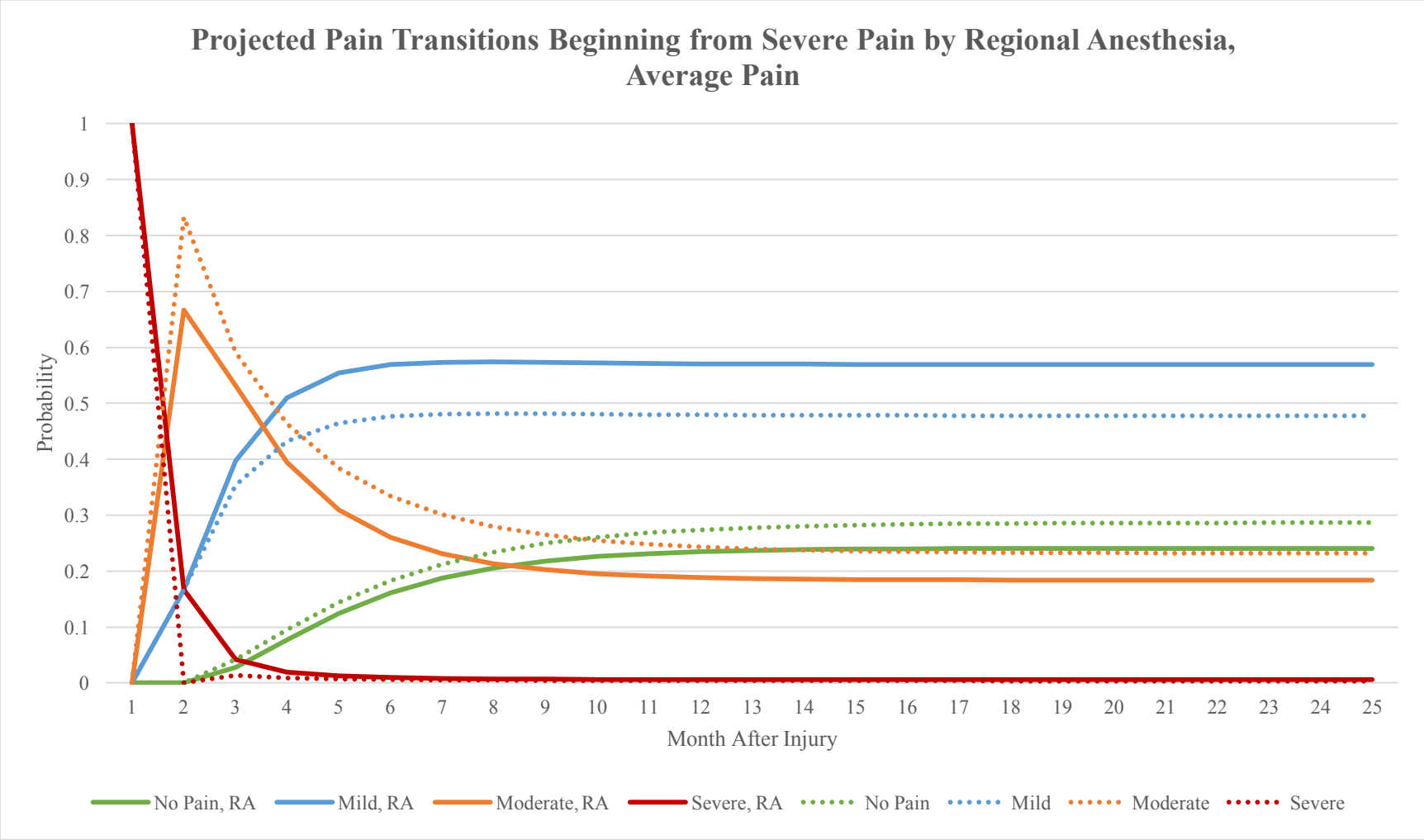
Based on distributions in Table 4-3 probability of being in a pain state after 24 monthly transitions, by RA

Figure 4-10: Projected Pain Transitions Beginning from Severe Pain by Regional Anesthesia, Worst Pain



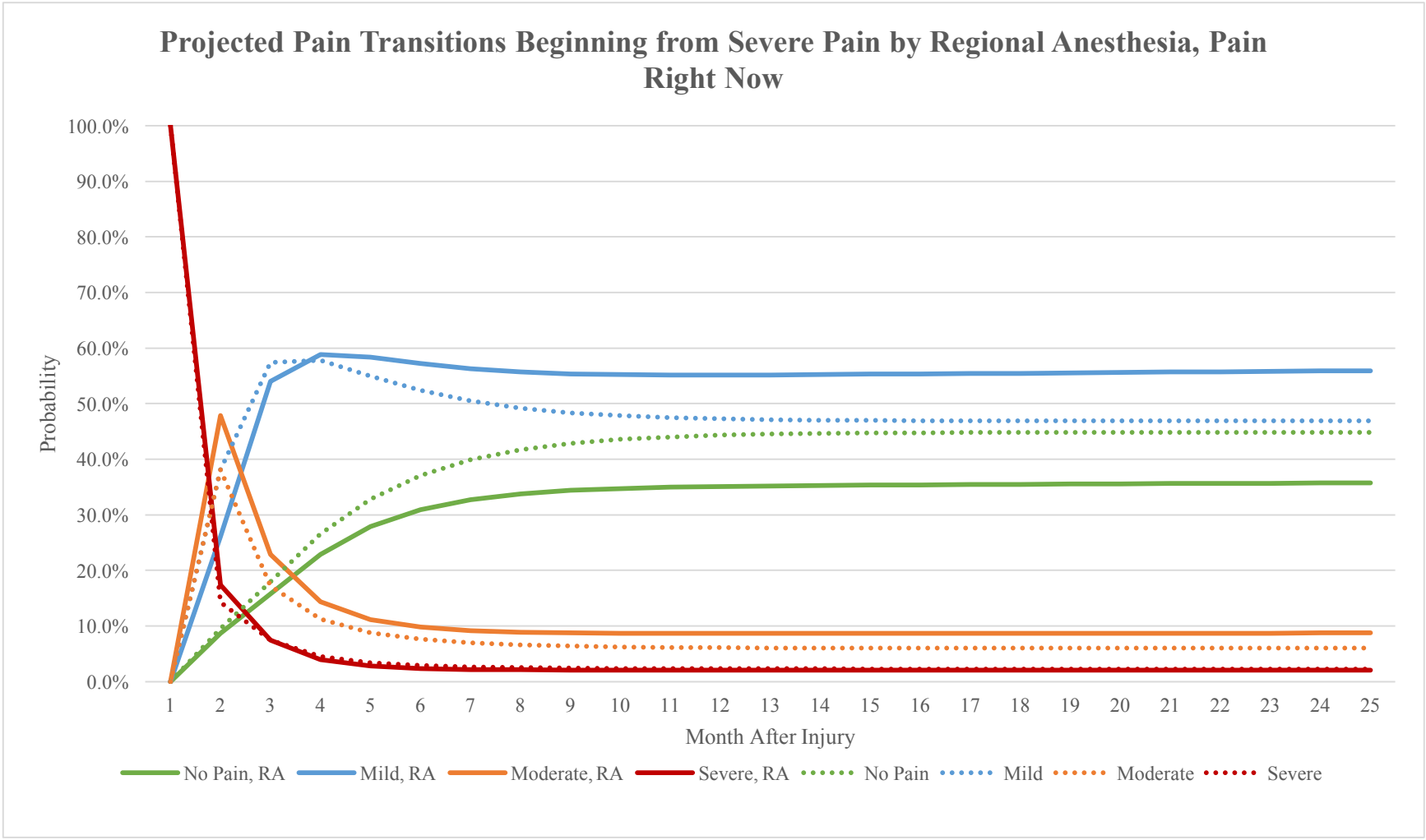
RA= regional anesthesia; *If everyone starts in "Severe Pain" probability of being in a pain state after 24 monthly transitions, by RA*

Figure 4-11: Projected Pain Transitions Beginning from Severe Pain by Regional Anesthesia, Average Pain



RA= regional anesthesia; *If everyone starts in "Severe Pain" probability of being in a pain state after 24 monthly transitions, by RA*

Figure 4-12: Projected Pain Transitions Beginning from Severe Pain by Regional Anesthesia, Pain Right Now



RA = regional anesthesia; *If everyone starts in "Severe Pain" probability of being in a pain state after 24 monthly transitions, by RA*

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Appendix

Below, X_n is a general discrete time Markov chain with a transition matrix, $p(i,j)$, for any state between $i\ and\ j$

$$P(X_{n+1} = j\ |X_n = i.X_{n-1} = i_{n-1}, \dots, X_0 = i_0) = p(i,j)$$

In other words, the probability of moving from one state to another state, in one time cycle, is only dependent on the present state, thereby making the past transitions irrelevant.

CHAPTER 5

Discussion

Adequate pain management after combat-related injury is essential to ensure optimal physical and mental health recovery. While multimodal pain management using regional anesthesia (RA) was a vital component of the military's pre-hospital and acute care pain management protocol for personnel injured in OEF/OIF conflicts, the long-term benefits of RA have not been well-researched in this population. Therefore, the overall goal of this dissertation was to use a biopsychosocial perspective to identify the complex and interrelatedness of pain and post-traumatic stress disorder (PTSD) symptom severity while also evaluating the short- and long-term associations of early pain management after combat related-injury on pain intensity and interference. Chapter 2 of this dissertation synthesized presentations of pain, PTSD, and depression after combat-related injury and highlighted that timely pain management, in addition to controlling acute pain, is associated with reduced mental health symptoms after polytrauma. Informed by the established relationship between pain and mental health symptom presentations in combat-injured military personnel and veteran populations, Chapter 3 evaluated the association of RA and PTSD symptom trajectories with pain intensity and interference in a sample of combat-injured OEF/OIF military personnel and veterans. Chapter 4 examined pain trajectories after combat injury in a probabilistic manner, while stratifying by early RA receipt status.

This dissertation contributes to the existing knowledge of providing adequate pain management for combat-injured military personnel and veterans while assessing the optimization of analgesic and anesthesia delivery via RA, which will inform future

research. The ability to expand science in the use of early aggressive acute pain management with RA, and its impact on long-term pain outcomes will be invaluable for future trauma responders and clinicians managing acute pain to prevent the development of chronic pain and possible disability.

Major Findings of Chapter 2

There is a paucity of studies examining the interrelatedness of pain, PTSD, and depression associated with combat injury. This integrative review of twenty-two peer-reviewed publications examined the complex relationship between pain, PTSD, and depression in combat-injured veterans and military personnel who served in OEF/OIF. Findings indicated that greater pain severity poses risks for developing PTSD following combat injury in this specific population. Moreover, early pain management may lessen the risk for developing PTSD. Following combat injury, depression can be a comorbidity of and a contributing risk factor to PTSD. The foundation of cross-sectional research examining pain, PTSD, and depression symptoms highlights the need for further analysis of these longitudinal relationships in combat-injured military personnel and veterans.

The body of literature in this integrative review examining clinical presentations after combat injury demonstrated a compelling demand for improvements in the continuity of assessments of pain and mental health symptoms across transitions in care. There are limited longitudinal studies investigating the prolonged surveillance of symptoms after combat-related injury that is further hindered by limited use of standardized assessment tools. The cross-sectional nature, on which existing research is built upon, does not account for the time since initial injury or consider the utilization of repeated patient-reported outcome measures across settings where combat-injured veterans access health

care. Future research efforts should include ongoing assessments with standardized measures in studies that investigate the relationship of pain and mental health beyond acute care and throughout recovery.

Major Findings of Chapter 3

This secondary analysis was one of the few longitudinal studies examining the association of early acute pain management, PTSD symptoms and pain outcomes after combat-related injury. Findings highlighted the positively correlated monotonic association between PTSD symptom severity and, pain intensity and interference up to twenty-one months after combat injury. Individuals receiving RA experienced lower pain intensity, even after controlling for injury severity and time from injury to observation using a mixed effect model. This association suggests that the delivery of analgesics and anesthetics using peripheral nerve blocks or epidurals improve short- and long-term pain intensity and interference after combat injury. Moreover, PTSD symptom trajectories, specifically military personnel and veterans with worsening PTSD, are associated with small statistically significant increases in average pain intensity and pain right now. This emphasizes the value of RA in the immediate after math of injury and throughout recovery. There is a need for continued evaluation of pain-related outcomes and comprehensive mental health treatment approaches beyond one year after injury. The association between pain and PTSD symptom trajectories, following combat injury, can inform providers that fluctuation is PTSD requires extensive assessments of pain intensity.

Major Findings of Chapter 4

In order to effectively manage acute pain intensity after injury, timely and targeted pain management is essential; however, less is known regarding how pain management interventions influence future post-injury pain trajectories. Efforts to evaluate pain trajectories after combat injuries are further impeded by missing data and possibly that personnel are lost to follow up as they transition out of their active duty military roles and back into their communities. A Markov chain approach was used to generate probabilistic transition matrices of pain trajectories after combat injury across multiple dimensions of pain intensity. The rationale for this using approach includes the capability of Markov models to explicitly account for the timing of events and state transitions, whereas time is often less explicitly accounted for in standard decision trees and clinical trials. This allows for modeling beyond the duration of the study data collection period. Findings from this secondary analysis showed that both RA and systemic pain management approaches were effective in reducing length of time spent in severe and moderate pain intensity after injury. There were more pronounced changes in the first six months after injury with individuals expected to have higher probabilities to move from states of high pain intensity, encompassing severe and moderate pain, to stabilize in states of mild or no pain, compared to beyond six months. This work provides the necessary underlying probabilistic parameters on which to build future simulated Markov models that incorporate costs and quality of life after injury to determine clinical and cost-effectiveness.

Limitations

It is important to note several limitations of this dissertation. The study's secondary nature hinders the ability to demonstrate causation of RA to improve pain intensity or interference. It does however, afford an important opportunity to examine the associations between early pain management approaches, PTSD symptom trajectories, and pain outcomes. The RAMBPOS dataset is the only longitudinal investigation of comprehensive patient-reported outcomes from the time of acute care and up to two years after combat injury. Therefore, this observational approach is a rare opportunity to evaluate how RA administration is associated with changes in pain intensity. This research did not examine the specific symptom criteria of PTSD, but instead examined total symptom severity and, uniquely, PTSD trajectories after combat injury. Changes to diagnostic criteria for PTSD assessment tools, such as the PCL-M, since the RAMBPOS data collection period makes it impossible to evaluate new diagnostic criteria (i.e. alterations in cognitive states and mood). Despite this challenge, the PCL is widely used in the literature and updated DSM-5 PCL instruments perform similarly in accurately capturing the prevalence of PTSD in OEF/OIF veterans.[1] The RAMBPOS was exclusively comprised of OEF/OIF military personnel and veterans, however findings of this research can inform the acute pain management care needs of civilian polytrauma cohorts. The symptom trajectories of civilian survivors of trauma and the effects of acute pain management interventions have not been extensively studied beyond acute care discharge. Civilian trauma care can be more comprehensive, in a way that accounts for the longitudinal trajectory of pain and mental health symptoms from the time of injury and throughout acute care. Developing adequate pain management protocols in trauma

care with long-term optimal recovery in mind will depend on leveraging findings from pre-existing datasets of patient-reported outcomes from injured military personnel and veterans. Moreover, the ability to expand science in the use of early aggressive acute pain management with RA, and its impact on long-term pain outcomes can be invaluable for future trauma responders and clinicians in civilian settings.

Implications

Implications of this research include the continuation of leveraging research of military advancements for trauma related pain to meet the pain management needs of severely injured civilians. The measures taken to ensure preservation of life after complex injuries require innovations of care commensurate with the extensiveness of bodily harm. Therefore, advancements made in trauma care are inextricably linked to war.[2] This includes the many modern clinical interventions used in civilian trauma care, which originated from the military. These trauma care improvements include the use of tourniquets to reduce mortality from hemorrhage, effective antimicrobial use for wound care to prevent infection, and helicopters for rapid transport after trauma in civilian health systems.[2,3] The use of these care advancements and other technical developments (e.g. protective body armor) have enabled trauma providers to preserve life after devastating injuries. In spite of the severity of injuries, case fatality rates among American military personnel are half those seen in previous armed conflicts (7.1%, OEF/OIF; 15.8%, Vietnam War).[4,5] The improved survival of critically ill trauma patients necessitated greater attention be paid to pain management from the point of combat injury and beyond throughout OEF/OIF. The delivery of multimodal anesthesia and analgesia via peripheral nerve blocks (i.e. RA) have been efficacious in the current military conflicts in providing

adequate and safe uninterrupted pain management after polytrauma and reducing future chronic pain intensity, as seen in this dissertation.

Other trauma care advancements, including RA for continuous optimal multimodal pain management, have had less penetration into the civilian sector. The use of indwelling nerve catheters has transformed pain control for combat-related extremity injuries since the Vietnam War.[6] Up to 57% of OEF/OIF military personnel with combat-related extremity injuries receive pain management in the acute care period via RA.[6,7] Unfortunately, RA techniques have not been widely incorporated within civilian emergent care settings.[8] In the 2016 report titled, *A National Trauma Care System: Integrating Military and Civilian Trauma Systems to Achieve Zero Preventable Deaths After Injury,*[8] the National Academy of Medicine identified:

> "Lessons learned by U.S. military personnel that improve the care and recovery of service members injured on the battlefield have been neither thoroughly nor adequately disseminated throughout the military, nor have they been translated reliably into civilian trauma care. The result has been many thousands of instances of preventable death and **needless disability** across the two sectors, along with excessive costs"[9]

The demonstrated success of RA for pain management in the combat theater, in transport, and throughout surgical and acute care cannot be neglected in the interwar period.[10-12] The ability to expand science in the use of early aggressive acute pain management with RA, and its impact on long-term health outcomes, will be invaluable for future trauma responders and clinicians managing acute pain to prevent the development of pain, pain interference and associated disability after serious injury. Civilian care and military personnel and veteran trauma care do not exist in silos.

Now more than ever, it is necessary to translate military trauma pain care into the civilian healthcare sector as domestic terrorist attacks and mass shootings produce

injuries akin to those of battlefield trauma. The increasing incidence of domestic mass casualty incidents, including the horrific events at the Boston Marathon (Massachusetts, 2013), Orlando Night Club (Florida, 2016), Las Vegas (Nevada, 2017), and Marjory Stoneman Douglas High School (Florida, 2018), calls for urgency in adopting military casualty pain care. Despite the surge in lethality of these recent attacks, it is important to recognize that there are many more survivors. These survivors can possibly suffer from devastating and debilitating injuries that would benefit from early aggressive pain management in similar ways to military combat pain care. For example, retrospective profiles of wound patterns in civilian public mass shooting incidences identified that as much as 20% of victims sustain extremity injuries.[13] Pain has been found to effect up to 50% of severely injured civilians nearly three years after acute trauma care.[14] Additionally, as much as 23% to 28% of injured civilians requiring trauma care develop PTSD within one year of injury.[14,15] The frequency of these events and severity of injuries sustained by survivors require trauma providers be able to provide timely pain management interventions.

The frequent co-occurrence of pain and PTSD after injury elicits a need for dual management of conditions throughout injury related care, beginning in pre-hospital and acute care. Uncontrolled pain and increased pain after injury is associated with an increased risk for developing PTSD.[16-18] Further, immediate pain management in combat-injured military populations is associated with reduced risk of developing PTSD after injury.[19] Clinical presentations of pain and PTSD after injury, coupled with the continued necessity of administering optimal analgesic medication in acute trauma care settings, furthers the need for exploration of using RA for providing adequate pain

control. Additional research is needed investigating how pain trajectories can influence future mental health symptom severity. This dissertation found that the application of RA and systemic pain management approaches reduce the amount of time spent experiencing high pain intensity and reduce long-term pain intensity after experiencing severe injuries. It is imperative that clinicians and researchers continue the translation, implementation, and evaluation of RA in civilian trauma settings.

Future Directions

Advancing the use of RA in civilian trauma care settings will require continued longitudinal research of severely injured persons and expanded opportunities for anesthesia and pain management providers to be trained in RA techniques. Future research in this line of inquiry must recognize the importance of the relationship between physical symptoms and psychological symptoms, as framed by the Biopsychosocial Model for Chronic Pain, after injury. Therefore, assessment of pain and mental health symptoms that extends beyond acute trauma care is essential to expand current knowledge of how findings from this research relate to civilian populations. Additionally, further prospective research examining the effects of RA on PTSD symptom severity, specifically if there is an association with a reduction in symptoms. These future investigations will require that patient-centered trauma care combine immediate survival treatment with consideration of long-term needs of pain management and mental health support. Doing so will depend on injured civilians having access to effective pain management approaches, such as RA. This requires coordinated efforts within health systems to ensure anesthesia providers are appropriately trained in RA administration.

Findings from this research may have the ability to advance the science to promote the science behind the care of certified registered nurse anesthetist (CRNA) led RA treatments for all traumatically injured persons. CRNAs are well positioned in many acute trauma care settings and can leverage their clinical training to incorporate effective pain management across the continuum of care for injured persons.[20] However, the proportion of time spent in of training for anesthesia providers to practice administering RA has not expanded since 1990[21] even as the number of patients requiring care for severe injuries has increased and as have the total associated costs in the United States (U.S.).[22] In light of this growing proportion of injury survivors and swelling costs of both pain and trauma in the U.S., there is a compelling need to determine the clinical and cost-effectiveness of RA after injury.[22,23] Future work evaluating the cost-effectiveness of RA over systemic analgesia after injury is necessary to advancing trauma care. Demonstrating the effectiveness of CRNA led RA administration has the potential to support policies expanding training opportunities and scope of practice for CRNAs in order to optimize pain management for injured persons.

Conclusion

In conclusion, this dissertation contributes to current understandings in the short- and long-term care requirements of combat-injured military personnel and veterans serving in OEF/OIF. There is a complex relationship between pain and mental health symptoms, specifically, PTSD, after serious combat injury. There is a significant positive relationship between patient-reported pain outcomes, both pain intensity and interference, and total PTSD symptom severity up to twenty-one months after combat injury. Worsening PTSD symptom trajectories are associated with experiencing more intense

average pain and pain right now after combat injury compared to individuals with improving PTSD trajectories. Individuals receiving RA experience less intense pain after injury than individuals not receiving RA. Markov modeling projected pain trajectories individuals may experience after combat-related injuries. Moreover, when stratified by receipt of RA and systemic pain management approaches there is a pronounced movement from high pain intensity to low pain intensity in the first six months after injury. This dissertation highlights the importance of sustaining efforts to monitor and manage pain among severely injured military personnel, veterans, and civilians.

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